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Subscription Information
Journal of The Association of Physicians of India is published monthly. The annual subscription is ₹ 12,000 (India) and US $ 500 (other countries). The Journal is dispatched within India by surface mail and to other countries by sea mail.

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Printed, Published and Edited by Prof. Milind Y. Nadkar, on behalf of The Association of Physicians of India, Journal of The Association of Physicians of India, Turf Estate, Unit No. 006 & 007, Opp. Shakti Mill Compound, Off Dr. E. Moses Road, Near Mahalaxmi Railway Station (West), Mumbai-400 011. Editor-in-Chief: Prof. Milind Y. Nadkar

Advertorial Enquiry:
Prof. Milind Y. Nadkar, Editor-in-Chief, JAPI, No. 006 & 007, Turf Estate, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai-400 011. Tel.: (022) 6666 3224 / 2491 2218 Mobile : 77381 85750 E-mail: onlinejapi@gmail.com / api.hdo@gmail.com

Printed at Shree Abhyudaya Printers, A2/210, Shah & Nahar Industrial Estate, Lower Parel (West), Mumbai 400 013. Tel.: (022) 2494 5863 * urvi@urvi.cc

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Tocilizumab or no Tocilizumab - To be or not to be

Yojana Gokhale

In COVID-19 cytokine storm, IL-6 is reported to play an important role. Tocilizumab, an antibody against IL-6 receptor, which is FDA approved for CAR-T cell therapy induced cytokine storm was thus used in COVID-19 cytokine storm and was reported to be beneficial in reducing mortality. Cytokine storm occurs in the second week (8th-14th day) of COVID and is characterized clinically by fever with hypoxia and hypotension with multisystem organ failure (if left untreated). Inflammatory markers like CRP, LHD, Ferritin are elevated. In Covid-19, hypoxia can occur due to cytokines triggered ARDS and/or pulmonary thromboembolism due to cytokine triggered coagulopathy. Tocilizumab does not improve coagulopathy.

Till date 5 Randomised Control Trials (RCTs) and many non-randomized cohort studies are reported on tocilizumab in Covid. Observational studies reported tocilizumab to be effective in reducing mortality in Covid19, but results from randomized control trials are contradictory. All RCTs included patients with saturation <94% or PaO2/FiO2 less than 300 (or between 200-300) and/or mild ARDS by definition. Thereby implying tocilizumab is probably not effective in reducing mortality in COVID cytokine storm with mild ARDS (PaO2/FiO2 between 200-300).

1. In BACC Bay (randomized, double-blind, placebo-controlled, N=242, T-161, C-81) trial, Stone et al reported that Tocilizumab was not effective in reducing need for ventilator or death by 28 days. In BACC trial, 16% patients did not require supplemental O2, 80% required less than 6L per min. O2. Though average saturation and PaO2/FiO2 ratio is not mentioned, over 90% patients had mild disease severity. In the sample size calculations for this trial, the authors assumed an event rate for the primary outcome of 30% in the placebo group and 15% in the tocilizumab group. However, only 11.2% patients had a primary-outcome event 7.8% were intubated and 3.3% died. This represents an event rate that was lower than anticipated for both groups, which is likely to have limited the ability to discern a treatment effect. If anticipated effect is small, then the sample size required is large. The hazard ratio for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% confidence interval [CI], 0.38 to 1.81; P=0.64). Authors have not ruled out possibility of some benefit or harm due to wide CI, though tocilizumab was not effective for preventing intubation or death.

2. In CORIMUNO-TOCI-19 (open label RCT, N=121, T- 64, C-67) by Hermine et al, patients with PaO2/FiO2 200-300 were included, whereas those from ICU/ on High Flow Nasal Canula (HFNC)/ Non-Invasive Ventilator (NIV)/ mechanical ventilator (MV) were excluded. On 14th day 12% reduction in need for MV or death was reported, but no reduction in death on day 28.

3. In RCT-TCZ-COVID-19 (open label RCT, N=126, T-60, C-66) by Salvareni et al included patients with PaO2/FiO2 200-300, average being 264, with average CRP 8.2, there was no benefit in achieving primary outcome (death/MV/ PaO2/FiO2<150) with tocilizumab. In this study among the 17 patients reaching one primary endpoint (PaO2/FiO2 <150) in the standard care group, 14 received tocilizumab as a rescue therapy (as per protocol). At 30 days, the incidence of intubation and death was comparable between the 2 groups. One can infer that the early administration of tocilizumab does not provide any significant advantage in reduction of intubation or mortality over a deferred administration at PaO2/FiO2 ratio less than 150mmHg.

4. In COVACTA trial (randomized, double-blind, placebo-controlled, N=438, T-294, C-144), which reported no mortality benefits on 28 day with tocilizumab, eligibility criteria were broad, viz. patients with saturation less than 94% on room air, which also enrolled 37% patients on MV. There was no stratification of severity.

5. EMPACTA, a randomized, double-blind, placebo-controlled, N=389, T-249, C-128, included patients with saturation less than 94% at room air. In EMPACTA trial, with similar inclusion criteria as COVACTA, the subject population included was minority groups (blacks, Hispanics, Asians), who have higher risk of death, 44% reduction in need for mechanical ventilator or death was reported.

None of the RCTs reported increased incidence of infection or serious adverse events in tocilizumab as compared to control arm.

Observational studies in which patients had moderate to severe hypoxia reported mortality benefit with tocilizumab.

1. At our center, in a retrospective analysis of 151 treated with tocilizumab and comparison with historic controls (who did not receive tocilizumab, N=118) of Covid patients with saturation 94% or less on supplemental Oxygen of 15 L per minute through non-rebreathing mask or PaO2/FiO2 ratio of less than 200, on multivariate Cox regression analysis, independent predictors of survival were use of tocilizumab (HR 0.621, 95% CI 0.427-0.903, P 0.013) and higher oxygen saturation. Our limitation being no propensity matching was done. Though tocilizumab cohort was 2 yrs younger (53yr), than control group (55yrs), it had more severely hypoxic patients too (86% v/s 91% saturation, P=0.001)

2. In a retrospective observational study in COVID 19 patients treated in ICU in New Jersey, Noa et al reported 49% mortality in 210 patients treated with tocilizumab and 61% mortality in 420 patients who did not receive tocilizumab.

3. Though Guaraldi et al included
patients with saturation <94% on RA or PaO2:FiO2 <300, average PaO2/ FiO2 ratio in their study was 169 in tocilizumab group as against 277 in standard care group. They also reported the effect of tocilizumab was at least two times higher in people with a baseline PaO2/FiO2 ratio of less than 150 mm Hg, implying that the benefit of tocilizumab could be greater in patients with a greater risk of death or mechanical ventilation.\textsuperscript{7}

4. In STOP-COVID trial\textsuperscript{13} (large multicenter observational comparative study from USA, in ICU admitted Covid-19 patients receiving tocilizumab within 48 hours of ICU admission versus non-tocilizumab cohort, with 419 and 3492 patients respectively after inverse probability weighting to match baseline characteristics and severity of illness, retrospectively analyzed), Gupta et al, reported 28.9% mortality in those treated with tocilizumab and 40.6% in not treated with tocilizumab. During a median follow-up of 27 days, patients treated with tocilizumab were reported to have a lower risk of death compared with those not treated with tocilizumab (HR, 0.71; 95%CI, 0.56-0.92), and on stratification as per severity of hypoxaemia as PaO2/FiO2 ratio on ICU admission (HRs, 0.88 [95% CI, 0.58-1.35] for ≥200 mm Hg or no mechanical ventilation and 0.59 [95% CI, 0.43-0.81] for <200mmHg and mechanical ventilation.

RECOVERY trial\textsuperscript{14} found that dexamethasone reduces mortality in hospitalized patients with COVID-19. The beneficial effect of dexamethasone was particularly pronounced in patients receiving invasive mechanical ventilation. These early data suggest that medications targeting dysregulated inflammation may be a promising therapeutic strategy among critically ill patients with COVID-19. But in published randomized control trials on tocilizumab in Covid19, the effect of tocilizumab on mortality are discordant with the results of observational studies. Possible reasons could be study design, different study population, severity of illness and timing of administration of tocilizumab.

In a meta-analysis by Tleyhej et al\textsuperscript{15} which included 5 completed RCTs (1325 patients) and 18 cohort studies (9850 patients), authors report Cumulative moderate-certainty evidence shows that tocilizumab reduces the risk of mechanical ventilation in hospitalized COVID-19 patients. While RCTs showed that tocilizumab did not reduce short-term mortality, low-certainty evidence from cohort studies suggests an association between tocilizumab and lower mortality. The authors state that the sample size required for an RCT to detect an RR of 0.75 for mortality with tocilizumab (with 80% power and a 0.05) is 4506 patients (2253 in each arm).

The total number of patients in the five RCTs is 772 patients in the tocilizumab group and 553 patients in the control group.

Press release from ongoing REMAP-CAP trial\textsuperscript{16} on 19th November stated tocilizumab was 99 per cent more likely to reduce deaths and time spent in intensive care among critically ill patients with severe COVID-19, compared to patients who did not receive the treatment. REMAP-CAP trial inclusion criteria are patients admitted to ICU with severe pneumonia requiring respiratory support such as high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation and COVID-19 infection confirmed by microbiological testing or where a multidisciplinary team has a high level of confidence that the clinical and radiological features suggest that COVID-19 is the most likely diagnosis. On 25th November, Interim position statement\textsuperscript{17} given by NHS England is, ‘until the full data from the REMAP-CAP and RECOVERY trials are available, the off-label use of tocilizumab within critical care should follow the criteria and information described in this interim clinical position. The trial Data and Safety Monitoring Board (DSMB) has determined that it is ethically imperative to withdraw the standard-of-care control arm of the immune modulator domain of the REMAP-CAP trial.’

Two RCTs viz. BACC (USA)\textsuperscript{4} and RCT-TCZ-COVID-19 (Italy)\textsuperscript{2} reported 3.3% and 2.4% mortality respectively. Whereas reported mortality for hospitalized Covid-19 patients in USA\textsuperscript{18,19} and Italy\textsuperscript{20} is 9.1-22.6% and 29.7% respectively, implying thereby that these RCTs enrolled mild cases of Covid-19 for tocilizumab usage.

We eagerly await the final results of REMAP-CAP and RECOVERY trial. Until such time, for patients of Covid-19 with moderate to severe hypoxia (PaO2/FiO2 less than 200), the judicious and timely use of tocilizumab, is a viable and probably lifesaving treatment of choice.

References

Itolizumab Treatment for Cytokine Release Syndrome in Moderate to Severe Acute Respiratory Distress Syndrome Due to COVID-19: Clinical Outcomes, A Retrospective Study

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Abstract
Background: Hyperinflammation, hypercoagulation and multi-organ dysfunction are life-threatening complications needing immediate attention in moderate-to-severe COVID-19 patients. Present our real world experience with Itolizumab, a repurposed immunomodulatory monoclonal antibody, administered in COVID-19 patients.

Methodology: Data from 25 confirmed moderate-to-severe COVID-19 patients, with high levels of pro-inflammatory markers and pulmonary function worsening on best supportive care and Itolizumab were included in this analysis. Patients requiring invasive mechanical ventilation were excluded. Clinical parameters (oxygen requirement) and laboratory parameters (ferritin, interleukin [IL]-6, C-reactive protein [CRP] and absolute lymphocyte count [ALC]) were studied pre-and post-treatment. Average total length of stay in hospital and ICU, percentage of patients requiring ICU admission and average time taken for weaning off oxygen for all patients were also reported.

Results: All Patients were in the range of 30-78 years of age, with majority being male (76%). Most prevalent comorbid conditions were diabetes (64%) and hypertension (28%). Median IL-6 value showed a decline by 85.4%. Significant reduction in median CRP (86.96%) and Ferritin (55.61%) was observed post-Itolizumab compared to pre-dose values. Median ALC improved from 1605 cells/mm3 (pre-dose) to 2462.5 cells/mm3 (post-dose). Average recovery time, defined as time from Itolizumab infusion to discharge was 9.28 ± 4.04 days. Average duration of hospitalization and ICU admission was 14.24 ± 4.15 and 8.27 ± 4.47 days, respectively, with 76% patients recovered and discharged. Median oxygen saturation improved from 88 % (pre-dose) to 96 % (post-dose). All patients were weaned off oxygen within Avg + SD : 6.53 ± 2.09 days post-Itolizumab treatment. One and two point reduction in ordinal scale was observed in 88% and 76% patients, respectively. Three patients (12%) did not show improvement in ordinal score of which two patients died because of complications due to pre-existing comorbidities. The all-cause mortality of 8%; was considered not related to Itolizumab. One infusion related event reported abated with infusion period extension.

Interpretation and Conclusion: A single dose of Itolizumab accelerated recovery in adult patients with COVID-19 by controlling immune hyperactivation. The clinical improvement was demonstrated by reduction in inflammatory markers, weaning off oxygen, reduced length of hospital stay and improvement of ordinal score. Itolizumab was well tolerated and when administered in the early phase of the inflammatory cascade is an efficient therapeutic option for treatment of cytokine release syndrome in moderate to severe COVID-19 patients.

Introduction
Since the SAR-CoV-2 (COVID-19) outbreak, the number of confirmed cases have exceeded 21 million with a mortality of 0.7 million. About 15-20% of the infected patients develop severe hypoxemia and require hospitalization2 and may progress to life-threatening complications such as acute respiratory distress syndrome (ARDS), systemic hyperinflammation, vascular hypo-responsiveness, increased endothelial permeability, hypercoagulation and multi-organ dysfunction.3 ARDS may lead directly to respiratory failure and is reported to be the cause of death in 70% and cytokine storm in 28% of fatal COVID-19 cases.

T-cells play a crucial role in viral clearance and regulate the activation, proliferation, and effector functions of a wide range of immune cells for the maintenance of self-tolerance and homeostasis.4 However, studies have shown that high serum concentration of IL-2, IL-2R, IL-6, IL-7, IL-8, IL-10, GM-CSF, IP-10, MCP1, MIP1a and TNF-α has been reported in moderate to severely ill COVID-19 patients admitted to the ICU,5 suggesting an immune dysregulation and brewing of a cytokine storm.

CD6 is a transmembrane glycoprotein associated with modulation of T-cell activation, proliferation, differentiation and trafficking.8 It is expressed on mature T-cells, thymocytes, B1a lymphocytes and CD56+ NK cells but not on T-regulatory cells8 and serves as a key checkpoint in regulating T effector cells that are crucial to autoimmune responses.10 The binding of CD6 to activated leukocyte cell adhesion molecule (ALCAM), a ligand of CD6 expressed on antigen-presenting cells, leads to T cell activation, proliferation, differentiation and survival.10

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Received: 21.09.2020; Accepted: 15.12.2020
Itolizumab is a non-depleting anti-CD6 humanized IgG1 monoclonal antibody that inhibits the activity and trafficking of T effector cells by selectively targeting CD6-ALCAM pathway. Late immunotherapy strategy to administer immunomodulatory agents, such as Itolizumab, can reduce the hyperinflammatory syndrome, also called Cytokine Release Syndrome (CRS), associated with COVID-19 complications.

Itolizumab is approved in India for chronic plaque psoriasis and is being evaluated in other immunoinflammatory disorders such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, uncontrolled asthma, lupus nephritis and acute graft-versus-host disease. Across studies and populations, Itolizumab is found to be safe and well tolerated. Previous studies have also demonstrated that Itolizumab downregulates T-cell activation, proliferation and subsequent production of various pro-inflammatory cytokines such as IL-6, TNF, IFNγ, IL-17 and IL-1.

Considering the paucity of clinical therapeutic alternatives for COVID-19 complications, we recommend treatment of COVID-19 related hyperinflammation using existing therapies with proven safety profiles to address the immediate need. Our experience presented here is based on the hypothesis that Itolizumab treatment with its immunomodulatory mechanism of action would control CRS and further reduce morbidity and mortality in moderate to severe COVID-19 patients.

Patients and Methods

We constituted an observational cohort in order to collect information about the impact of adding anti-CD6 monoclonal antibody, Itolizumab to the best supportive care in hospitalized patients on clinical course of COVID-19, recovery time and survival status. We included confirmed COVID-19 cases from 5th June 2020 up until August 22nd 2020 from two centers; 21 patients from Shri Markandeya Solapur Sahakari Rughnalya & Research Centre Niyamit and CNS Hospital Sholapur and 4 patients from Kashibai Navale Medical College, Pune. The inclusion criteria were a confirmed diagnosis of COVID-19, age > 18 years and inpatient admission with SPO2 < 94%. The exclusion criteria was patients on invasive mechanical ventilator.

Data was extracted on demographics, personal medical history, comorbidities presenting symptoms, concomitant medications and for outcomes from the hospital’s medical records. Outcomes included recovery time from hospital admission to day of discharge, average total length of stay during hospitalization and ICU admission, improvement in ordinal scores, average time taken for weaning off oxygen and mortality rates. All clinical outcomes were monitored until day of discharge.

For COVID-19 diagnosis, specimens were obtained by nasopharyngeal and oropharyngeal swabs under aseptic condition and tested with real-time reverse transcription polymerase chain reaction (rRT-PCR) assay. COVID-19 positive confirmed patients were administered standard of care such as antivirals (remdesivir/favipiravir), hydroxychloroquine, anticoagulants and steroids as per the hospital protocol. Based on the clinical assessment of patients at hospitalization, oxygen supplementation by nasal cannula, non-rebreather mask (NRBM), bilevel positive airway pressure (BiPAP) or pressure-controlled ventilation (PCV) was initiated. If the condition of patients deteriorated, they were intubated and put on invasive mechanical ventilator as per the hospital protocol. Patients who were hospitalized and needed oxygen support were included in this observational cohort, while those requiring invasive mechanical ventilation were excluded.

Patients (N=25) who displayed high levels of pro-inflammatory markers and showed deterioration in spite of best supportive care were administered single dose of 1.6 mg/kg Itolizumab infusion over a period of 5-6 hours. A premedication of 100 mg Hydrocortisone and 30 mg Pheniramine (i.v) was given 30 minutes prior to Itolizumab infusion.

Clinical parameters such as oxygen saturation, oxygen supplementation and changes in laboratory investigations [ferritin, IL-6, C-reactive protein (CRP), absolute lymphocyte count (ALC)] were recorded prior to and post Itolizumab administration. IL-6 levels were evaluated by electrochemical luminescence method. Ordinal scale developed by Word Health Organization (WHO) was used to measure the clinical improvement. Average time to recovery, defined as time from Itolizumab infusion to discharge, average total length of stay during of hospitalization or ICU admission and average time taken for weaning off oxygen for all patients, were calculated.

This retrospective study followed good clinical practice guidelines on clinical research and data protection.

Descriptive statistics was used to summarize the data; Baseline demographics and clinical characteristics were expressed as mean ± standard deviation (SD) or the median (min, max) for continuous numerical variables and the frequency (percentage) for categorical variables. In data analysis, N represents the number of patients with available values, excluding the missing data.

Results

The age of the patients ranged from 30 to 78 years (mean 52.04 years; Table 1). Seven patients (28%) were ≥ 60 years of age. Majority of the patients were male (76%). Patient’s comorbid conditions included diabetes (64%), hypertension (28%), deep vein thrombosis (4%) and hypothyroidism (4%). About 24% patients reported having both diabetes and hypertension, and 24% patients reported no comorbidities. Out of the 25 patients admitted to the hospital, 17 patients data was available on presenting complaints, while all patients had complaints of difficulty in breathing, 11(64.71%) presented with fever and cough.

All patients were on non-invasive ventilation: 36% on NRBM and 36% on BiPAP, 16% patients on nasal cannula and 12% patients on pressure-controlled ventilation (PCV). For outcome analysis in form of clinical and laboratory parameters last follow up values were considered as post dose values.

Nineteen patients were discharged with recovery rate of 76% and average recovery time of 9.28 ± 4.04 days. The average total length of stay during of hospitalization was 14.24 ± 4.15 days, data of four patients was censored as they were lost to follow up and two patients died. The all-cause mortality was 8%.
Among the 25 patients, 44% required ICU admission during hospitalization with average total length of stay of 8.27 + 4.47 days in ICU.

Median SpO2 levels improved from 88% (pre-dose) to 96% after administration of Itolizumab along with best supportive care (Figure 1). The average time taken from Itolizumab infusion to weaning off from the oxygen was 6.53 ± 2.09 days. Three patients (12%), of which two died and one of the four censored patients did not show any improvement in ordinal score. The remaining three of the censored patients showed at least one point reduction in ordinal score but were lost to further follow up.

A significant decrease in pro-inflammatory biochemical parameters such as ferritin, IL-6 and CRP was observed after treatment with Itolizumab. The median ferritin levels from pre-dose 829 (12, 2103) improved to post-dose 368 (180, 966) ng/mL with

### Table 1: Baseline characteristics and demographics

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reduction of 55.61 % (Figure 2). The IL-6 levels median from pre-dose 113 (48, 645) to post-dose 16.5(4.2, 44.3) pg/mL with reduction of 85.4%. (Figure 3). The CRP levels median from pre-dose 46 (13, 300) to post-dose 6 (0.6, 25) mg/L with reduction of 86.96% after treatment with Itolizumab (Figure 4). The median pre-dose ALC was 1605 cells/mm$^3$. These levels eventually improved to 2462.5 cells/mm$^3$ post treatment with Itolizumab.

Out of 25 patients, 3-point, 2-point and 1-point reduction on the ordinal scale were observed in 68%, 76% and 88% patients, respectively. The cumulative and patient wise changes in ordinal score and time to recovery during hospitalization is illustrated in Figures 5 and 6, respectively.

Best supportive care for all patients included anticoagulants, low molecular weight heparins- enoxaparin (100% of patients), short course of steroids-methylprednisolone (96% patients) antivirals -remdesivir or favipiravir (80% of patients) and hydroxychloroquine (20% of patients). A single case of infusion related reaction was reported of grade 1 severity presented with fever, chills and rigors. The patient received symptomatic treatment with pheniramine 30mg i.v and paracetamol. The rate of infusion was slowed down to 25 ml/hour for the remaining infusion.

The first patient who died was a 58-year-old male who had presented with symptoms of fever, cough, and dyspnea in the past 10 days. He had a history of diabetes. On admission, his SpO2 was 69%, IL-6 was 645 pg/mL, ferritin was 488 ng/mL, LDH was 612 U/L, TLC was 3800 cells/mm$^3$ and CRP was 14.2 mg/L. He was initiated on BiPAP FiO2 100% (SpO2 88%). On day 2, he continued on BiPAP (SpO2 90%) and received Itolizumab infusion (1.6 mg/kg). On day 3 of hospitalization, an improvement in clinical and laboratory parameters was observed with SpO2 of 96%, TLC 11800 cells/mm$^3$, CRP 12.7 mg/L and IL-6 44 pg/mL. He continued on BiPAP 100% FiO2. On Day 4, SpO2 was 94%, FiO2 80% and Chest X-ray showed slight improvement. On Day 5, SpO2 was 89% and the patient had a sudden Cardiac arrest and died in spite of CPR administration.

The second patient who died was a 78-year-old male who had presented...
with recent fracture of right femur and had a history of diabetes and hypertension. On admission, his SpO2 was 80% and was initiated on BiPAP. His pre-dose IL-6 level was 422 pg/mL, CRP was 110 mg/L, LDH was 1570 U/L and ferritin was 1500 ng/ml. He received Itolizumab infusion (1.6 mg/kg) on Day 3. He weaned off BiPAP 7 days post Itolizumab infusion and shifted to high flow nasal cannula. On Day 10, the patient had pulmonary embolism and atrial fibrillation and was again put on BiPAP. His condition however, deteriorated and he died on Day 14. Both these events were considered not related to Itolizumab.

**Discussion**

COVID-19 is rapidly spreading worldwide, sending billions of people into lockdown as hospitals struggle to cope. Efforts to identify new drugs that could help treat COVID-19 are underway. However, new drug development is impractical in the face of the current global pandemic. An effective alternative is repurposing an existing drug with known safety profile and showing effectiveness in managing COVID-19 complications. Itolizumab, approved in India in December 2012 for treating chronic plaque psoriasis, with its novel immune-modulating anti CD6 mechanisms is showing promise in addressing the severe immuno-inflammatory complications experienced by COVID-19 patients. It has recently received approval for restricted emergency use by Drugs Controller General of India’s (DCGI) for the treatment of cytokine release syndrome in moderate to severe ARDS in patients with COVID-19. We administered Itolizumab to patients who exhibited high levels of pro-inflammatory markers and showed deterioration in spite of being provided the best supportive care.

In COVID-19 infections, recovery and fatality rates vary between demographic groups, with certain comorbidities associated with a higher risk.22-24 Age, gender and comorbid conditions are considered as risk factors for severe COVID-19 illness, complications, and death. As per the systematic review and meta-analysis by Li J et al. (2020), the pooled mean age was 60 years among those with severe disease. Case fatality was highest in persons aged ≥85 years (range 10%-27%) followed by those aged 65-84 years (3%-11%) among the confirmed cases in USA.24 Other than older age, underlying medical comorbidities such as diabetes, hypertension, malignancy and immunosuppression, and male sex have been the identified biological vulnerabilities for more severe COVID-19 outcomes.22,24 In the current study, majority of the patients administered Itolizumab were male and the age of the patients ranged from 30 to 78 years. Diabetes and hypertension were the most frequently reported comorbidities. Two patients who died in this observational cohort both were elderly with 58 years and 78 years of age, both had diabetes and in addition, second patient had hypertension.

During the course of inflammatory diseases, increase in ferritin production has been observed.25 This may be due to ferritin secretion caused by the macrophages or due to several inflammatory stimuli including cytokines such as IL-6 which can induce ferritin synthesis.23 Interestingly, an elevation in IL-6 levels has been reported with the aggravation of the COVID-19 disease.26 Thus, hyperferritinemia is considered associated with inflammatory states in COVID-19 infection. As per a recent retrospective study with 150 confirmed COVID-19 cases, a significant difference in ferritin and IL-6 levels were observed between the non-survivor group and the survivor group (p < 0.001).27 CRP is a non-specific acute-phase protein induced by IL-6 and the levels increase rapidly and significantly during acute inflammatory responses.28,29 Individuals with CRP levels > 41.8 mg/L were more likely to develop COVID-19 complications.30 Elevated levels of all these parameters suggest that the mortality seen in severe COVID-19 cases with ARDS might be due to the virus-activated cytokine release syndrome. Two patients who died in this study also had high levels of IL-6 and Ferritin at baseline. This cytokine storm is characterized by a marked increase in interleukins and tumor necrosis factor that promotes lymphocyte apoptosis.31 A lymphocyte count <1.0 × 109/L has been associated with severe COVID-19 disease.32 During the disease course, evaluation of parameters such as ferritin, IL-6, CRP and lymphocyte count may help identify patients at risk of respiratory failure, help in triage planning and prompt intervention in order to improve outcomes. After administration of Itolizumab, a reduction in important indicators of disease severity such as ferritin, IL-6 and CRP levels were observed in the current set of patients. An improvement in lymphocyte count was also observed.

The severity of COVID-19 disease ranges from asymptomatic infection to severe illness characterized by ARDS. SpO2 level, in particular, is an important parameter to determine the need for admittance to ICU. Depending on the disease severity and clinical assessment of patients at hospitalization, oxygen supplementation by nasal cannula, NRBM, BiPAP or PCV was administered to all patients directly at hospital admission. An improvement in oxygen saturation (96% SpO2) and patient’s clinical status (2 or 3 points reduction on WHO ordinal scale)30 was observed post Itolizumab administration in majority of the patients. The patients were weaned off oxygen within an average of 6.53 days post Itolizumab administration with majority of the patients getting discharged 14 days (median) post hospitalization.

The median time to recovery, defined as time from Itolizumab infusion to discharge, was 8 days. In previous studies, median length of hospitalization among survivors has been observed to be 10 to 13 days34,36 and the median time to recovery with remdesivir has been seen to be 11 days.37 The median and mean length of stay for the 11 patients admitted in the ICU was 8 and 8.27 days, respectively in our study, as compared to the median length of stay for 15 days (Suleyman G et al, 2020) and mean length of stay for 18.4 days (Turacotte JJ et al, 2020).38,39 Depending on the study and characteristics of the patient population, a mortality rate of 39% to 72% has been reported among patients admitted to ICU with COVID-19 complications.5,36,40,41 In the current study, two patients died on Day 5 and Day 14 (one due to sudden cardiac arrest and another due to pulmonary embolism and atrial fibrillation, who got admitted with fracture femur); which was considered not related to Itolizumab administration. The all-cause mortality in the current study was observed to be 8%. A single event of infusion related reaction related to Itolizumab administration
was reported which was abated with the extension of infusion period. The patient received symptomatic treatment and completed the infusion.

Limitations of this study include its retrospective nature and the occurrence of missing data, which can be considered acceptable in this pandemic situation, as it is very difficult to record repeated observations and assessments while the hospital battles with managing the ever-growing numbers of COVID-19 patients.

Conclusion

A single dose of Itolizumab accelerated recovery in adult patients with COVID-19 by controlling immune hyperactivation. The clinical improvement was demonstrated by reduction in inflammatory markers, weaning off oxygen, reduced length of hospital stay and improvement of ordinal score. Itolizumab was well tolerated and when administered in the early phase of the inflammatory cascade is an efficient therapeutic option for treatment of cytokine release syndrome in moderate to severe COVID-19 patients. Randomized controlled clinical trials in large patient population can further validate these findings.

References

Liver Function Status in COVID-19: An Indian Perspective

Kheya Mukherjee¹, Abhra Banerjee², Debojyoti Bhattacharjee³, Suparna De⁴, Ajay Biswas⁵, Debanjan Garai⁶, Roopsa Chakraborty⁶, Asis Manna⁶

Abstract

Introduction: In SARS-CoV2 infection multi-organ involvement of heart, kidney, pancreas and liver are reported. Most studies suggest that though mild derangements of liver function may be experienced by most COVID-19 patients but significant liver injury is not common. The aim of this study was to describe clinical characteristics of COVID-19 patients admitted to this level 4 COVID hospital and find out their relation to the liver parameters.

Materials and Methods: COVID-19 patients admitted in this level -4 COVID hospital during the study period were classified as mild (Group 1, n=42), moderate (Group 2, n=40) and severe (Group 3, n=35) cases as per national guidelines. Serum samples were analyzed using biochemistry autoanalyzer. Serum levels of total and direct bilirubin, Alanine Transaminase (ALT) and Aspartate Transaminase (AST), Alkaline Phosphatase (alkp), total protein and albumin were assayed.

Results: Patients with higher BMI (Body mass index) had developed greater COVID-19 related complications and hence had to be admitted either in HDU (Group 2) or in ICU (Group 3) set up. Total and direct serum bilirubin levels were normal and almost similar in the various study groups. The primary liver enzymes ALT and AST were raised in the entire study population. However differences between the study groups were statistically insignificant. ALKP was within normal reference range for all the cases. Serum total Protein levels were within normal physiological limits in all the three groups. However serum albumin levels were reduced significantly in Groups 3 and 2 in comparison to Group 1.

Conclusion: Derangements of LFT in COVID-19 Patients are common especially in patients with severe disease but its long term impact is unknown. Hence, further investigation and long term follow up of recovered COVID-19 cases is warranted to understand the pathophysiology and implication of liver injury that occurs both in overt and covert forms during infection.

Introduction

An outbreak of COVID-19 caused by SARS-CoV2 was started in December 2019 in the Wuhan province of China. On 11th March, 2020 the WHO declared COVID-19 as a global pandemic disease.1 As on 15th November 2020, this pandemic has led to over 53.7 million confirmed cases and over 1.3 million deaths.2

SARS-CoV2 mainly affects respiratory system. Patients can experience a range of clinical manifestations, from no symptoms to critical illness. The common symptoms of COVID-19 are fever, cough, fatigue, shortness of breath, expectoration, myalgia, rhinorrhoea, sore throat, diarrhea, loss of smell and taste etc. According to illness severity SARS-CoV-2 infection can be grouped into the mild, moderate and severe categories.3,4

In SARS-CoV2 infection multi-organ involvement of heart, kidney, pancreas and liver are reported.5 Abnormal liver function test results are also reported in COVID-19 which might be due to liver damage by SARS-CoV2. Angiotensin-converting enzyme2 (ACE2) receptor is expressed on cholangiocytes of liver as well as in hepatocytes but its expression is much higher in cholangiocytes which may act as a potential route of entry for the virus in the liver leading to dysregulation of liver function.6,7 SARS-CoV2 induced hepatic damage can also be explained by immune mediated inflammation such as cytokine storm, pneumonia associated hypoxia and hypotension and drug hepatotoxicity.8,9

A study on postmortem liver biopsy of COVID-19 patients revealed moderate microvascular steatosis, mild lobular and portal activity.7

Most studies suggest that though mild derangements of liver function may be experienced by most COVID-19 patients but significant liver injury is not common.8

The effect of abnormal liver biochemistry of COVID-19 is unclear. Some studies found that there is significant association between elevated AST and ALT with the disease severity and mortality, whereas other studies did not find it.8

As little data about liver enzyme derangements and its clinical impact on COVID-19 patients is available, the aim of this study was to describe clinical characteristics of COVID-19 patients admitted to this level 4 COVID hospital and find out their relation to the liver parameters.

Materials and Methods

A descriptive observational study was conducted at ID&BG Hospital, Kolkata from 1st June 2020 to 31st August 2020. The study proposal was approved by Institutional Ethics Committee. Confirmed COVID-19 cases on basis of RNA RT PCR in nasopharyngeal and oropharyngeal swab samples, admitted in dedicated...
COVID-19 wards, HDU and CCU of ID&BG Hospital, Kolkata during the study period were included (n=117). Severity of COVID-19 was assessed as per the national guidelines and clinical management protocol for COVID-19 laid down by the Government of India Ministry of Health and Family Welfare Directorate General of Health Services. Patients were classified as mild (Group 1, n=42), moderate (Group 2, n=40) and severe (Group 3, n=35) cases based on symptoms and results from chest radiography and clinical examination. Patients with uncomplicated upper respiratory tract infection without evidence of breathlessness or hypoxia (normal saturation) were classified as mild cases. Moderate cases presented with features of fever, cough, dyspnoea, hypoxia (Sp0<94%) and high respiratory rate of 24 or more. Patients with severe pneumonia or adult respiratory distress syndrome (ARDS) with Sp0<90% on room air, respiratory rate greater than 30 breaths per minute and chest X-ray infiltrates and occurrence of respiratory or other organ failure that requires intensive care unit (ICU) monitoring and treatment were considered as severe.

Patients with underlying liver disease, including chronic hepatitis B and alcoholic or non-alcoholic fatty liver disease (NAFLD) defined by ultrasonographic detection or CT measurements of steatosis were excluded from the study. Patients with fever of any other infectious etiology like Malaria, Dengue, Chikungunya, H1N1 infection etc. were excluded from this study.

Detailed medical history was obtained from all the cases to assess the presence of co-morbid complications in corona affected persons.

Informed consent was taken and venous blood sample were collected aseptically in plain vials from each case after 12 hours of fasting. Serum separated following centrifugation was analyzed using a biochemistry autoanalyzer (Konelab-300). All samples were coded and assayed in a blind fashion by an investigator who was unaware of the participant’s clinical status. Serum levels of total and direct serum bilirubin levels were normal and almost similar in the various study groups (p values 0.68, 0.16 respectively). The primary liver enzymes ALT and AST were raised in the entire study population. However differences between the study groups were statistically insignificant. ALKP was within normal reference range for all the cases.

Serum Total Protein levels were within normal physiological limits in all the three groups. However serum albumin levels were reduced in Groups 3 and 2 in comparison to Group 1. The inter group differences were statistically significant (p value 0.001).

### Discussion

In admitted patients of COVID 19, liver dysfunction may be common and it seem to be more in severe cases of COVID 19. Severe liver injury leading to liver damage, liver failure or death were so far uncommon. Elevated levels of ALT and AST were reported in 16 to 53% of patients. Abnormal liver enzymes in COVID 19 patients were first reported by Chen et al from Wuhan. He had reported an increase in serum levels of ALT, AST and LDH in 43.4% of cases. In a study from China it has been reported that there is higher elevation of ALT and AST in severe disease (28.1%) compared to mild
cases (19.8%). Xu L et al in their study from Wuhan found abnormal AST in severe cases (39.4%) in comparison to mild cases (18.2%) and the incidence of liver injury in severe cases was also markedly higher (36.2%) than mild patients (9.6%). Another study from Northern Italy revealed alteration of LFT in 62.4% of patients. In half of these cases AST, ALT and GGT were elevated but reduced serum albumin levels was seen in 93.5% of cases. The current study results are in accordance with these findings. Elevated levels of ALT and AST were noted in all three groups of admitted COVID-19 cases. The rise were < 2 times the upper level of normal. The differences between the groups were statistically insignificant. Serum albumin levels were decreased in the current study groups and those admitted in ICU had the lowest values. Since the serum total protein levels were normal, the decrease in serum albumin may be inferred upon poor nutritional status of the patients developed during illness or prolonged stay in hospital. Studies from South East Asia like those from Kaushik A et al in their study in Uttar Pradesh, India showed that 59.04% of admitted COVID 19 patients had abnormal LFT with elevated AST in 45.71% and elevated ALT in 25.71%. A similar study from Pakistan by Asghar MS et al found the correlation between deranged values of LFT enzymes and increase number of ICU admission and mortality. They had quoted significantly elevated levels of GGT and ALP, while in contrast we had quoted significantly elevated levels of AST and ALT. Derangements of LFT, especially elevation of ALT and AST are observed in COVID 19 patients on admission and are seen in those with severe diseases but this does not lead to significant liver damage or failure. The pathogenic mechanism of altered LFTs are not clear but most likely it seems multifactorial including hepatocytotoxic and cholangiocytes infection, microthrombotic endothelialitis, immune dysregulation, drug induced liver injury and hepatic ischaemia related to hypoxia and ICU related infections. The liver injury seems to be self limiting and specific treatment is not necessary.

Abnormal LFT in COVID-19 is often transient and often simultaneously combined with increased enzymes from heart and muscle and it return to normal without any liver related morbidity and mortality. Aminotransferase elevation in COVID-19 may be also due to myositis similar to severe influenza infection. A recent study had hypothesised that SARS-CoV-2 binds directly to cholangiocytes demonstrating Angiotensin Converting Enzyme 2 (ACE) receptor and cause liver damage. This explains partially the contribution of SARS-CoV-2 infection to the liver dysfunction in our patients.

The limitation of this study is that the role of other factors like previous intake of medications, other undiagnosed liver disease was not established. Continuous follow up and serial estimation of LFT in COVID 19 effected individuals is required to derive any conclusive evidence of chronicity of this viral liver disease.

Conclusion

Derangements of LFT in COVID-19 Patients are common especially in patients with severe disease but its long term impact is unknown. Many explanations have been provided to describe these abnormalities but currently there is insufficient data to explain this phenomenon. Hence, further investigation and long term follow up of recovered COVID-19 cases is warranted to understand the pathophysiology and implication of liver injury that occurs both in overt and covert forms during infection.

References

2. Weekly epidemiological update – 17 November 2020 Data as received by WHO from national authorities; as of 10am CEST 15 November 2020.
3. Clinical Presentation of People with SARS-CoV-2 Infection.
Exercise Prescription in Diabetes- S.M.A.R.T.: A Prospective Study

Manoj Saluja¹, Drishya Pillai²*

Abstract

Background: Exercise prescription has always been a mandatory yet extremely under rated non-pharmacological approach in management of diabetes mellitus. SMART acronym for S – specific, M – measurable, A – attainable, R – realistic, T - time oriented, is a newly proposed idea for implementing the same with supposedly better results. We tried to analyse the results objectively by SMART prescription of individualized exercise regimes to patients along with medicines.

Methods: Single centred, prospective study conducted over a time span of 3 months, on 75 patients, with biweekly follow-up. At the end of three months, we evaluated the results (of 52 patients who remained) by comparing random blood sugar and glycosylated haemoglobin values of the patients at the beginning and end of the trial.

Results: A significant reduction in blood sugar (p-0.023) and A1C levels (p-0.105; ns) was noted after a period of three months; with an average reduction of 31mg/dl and 0.37% noted in each respectively.

Additional benefits of better follow up, reduced financial burden, increased compliance to the said regimen were observed.

Discussion: Recommending exercise and lifestyle changes is as important as pharmacological management in diabetes. A SMART approach, methodical prescription of the exercise routines and drugs- individualized for patients, will likely have better results and patient satisfaction. A practice of switching to precise written suggestions than verbal ideas and reviewing the progress on every follow up visit may improve the outcome.

Introduction

One critical focus in diabetes control and overall health improvement in individuals with diabetes and prediabetes is implementation of exercise. Reducing sedentary time and increasing physical activity throughout the day are equally important. The substantial role of exercise as a therapeutic tool in improving the quality of life of the patient, hitherto remains largely unexplored. There are multitudes of reasons responsible. To state a few, verbal and vague advices by the doctor, absence of any deadline-like a set goal or a set time frame and lack of instructions to help achieve the target are some of them. To do away with the discrepancies, a novel concept of S.M.A.R.T. was borrowed from Management to therapeutics for exercise prescription, with a surprisingly impressive output.

This study explores the said concept and evaluates the benefit on glycaemic control of diabetic patients.

Materials and Methods

Study design

A single centred, prospective, follow up study, conducted at the diabetes clinic, Government medical college Kota and associated hospitals. 75 participants were randomly selected for the study. Random blood sugar and glycosylated hemoglobin level was measured at the time of entry into the trial. Patients were prescribed physical exercises as per SMART acronym, were made to maintain a diary and were advised follow up after every two weeks. After three months, random blood sugar and HbA1c were measured again and a comparative analysis was done between the two set of values.

Care was taken to avoid any change in medication of the patient so as to avoid confounding factors.

Inclusion and exclusion criteria

Known case of diabetes mellitus type 2 on oral antiglycemic therapy or insulin.

Patients who had any of the following, were excluded:

Any coexisting illness like hypertension, coronary artery disease etc.

Patients lost to regular follow up

Patients whose medications had to be altered due to unavoidable circumstances.

Study statistics

At the end of three months, after excluding the ineligible patients, 52 patients remained. Continuous variables were expressed as means with standard deviation or medians and interquartile ranges or simple ranges, as appropriate. Categorical variables were summarized as counts and percentages. We used GraphPad Prism, version 8.4, for statistical analysis as well as to plot the map. Unpaired student t-test with unequal variances was used.

Results

On comparing the two sets of glycosylated hemoglobin values, we saw that majority of study participants...
had a reduction in HbA1c. This decline over the set period of three months, with an average of 0.37%, though statistically insignificant (two tailed p- 0.105), showed an interesting trend that can be further looked into. 47 patients had reduced values, two had no difference and three of them showed an increase Table 1.

While the average sugar control as estimated by HbA1c did not show a statistically significant decline; the random blood sugar levels did however reduce significantly. (two tailed p-value 0.023) with a mean reduction of 31.51 ± 15.2.

### Discussion

According to ADA, physical activity includes all movement that increases energy use. Exercise is defined as a planned, structured physical activity. Managing blood glucose varies with every person and hence, the recommendations, should be tailored to meet the specific needs of each individual. Recommendations are additional to, and not a replacement for, increased structured exercise and incidental movement. Various studies have been conducted, like the LOOK AHEAD trial, which prove that there is a significant reduction in weight, blood sugar levels, glycosylated haemoglobin, improvement in quality of life and even remission of the disease for some time.

Aerobic and resistance exercises are commonly preferred options with a notable improvement in A1C by 0.57%. Stretching and balance exercises increases range of motion around joints, flexibility, benefit gait and prevent falls.

These facts and statistics, along with their importance in diabetes management are not lost on physicians. Every treating doctor, either formally or informally, stresses on the significance of regular exercise, reduction of sedentary time, weight management and adequate dietary changes required. Unfortunately, a considerable gap still exists between the set targets and the achieved ones.

To do away with the discrepancies, a novel concept of S.M.A.R.T. was borrowed from Management to therapeutics for exercise prescription, and applied on a small set of patients attending the diabetes clinic.

The S.M.A.R.T. acronym helps, in a planned, systematic and patient friendly way, to increase the chances of achieving the set target or goal, with an additional advantage of enabling a tailor-made prescription. It stands for S – specific, M – measurable, A – attainable, R – realistic, T - time oriented.6 SPECIFIC implies a simply written goal, urging the doctor to define exactly what has to be pursued by the patient. It consists of 6Ws-WHO, WHAT, WHERE, WHEN, WHY, WHICH: Who is involved? What do you want the patient to accomplish? Identify the location. Where will the activity be done? Establish a time frame. Which are possible constraints and requirements? For instance, rather than saying “you should start walking”, a written instruction is prescribed, stating “Walk for at least 30 minutes every day for 5-6 days/week in the park nearby, to reduce 1 kg weight by the next visit, 1 month later”, it has a much greater chance of being accomplished. MEASURABLE implies, establishing a concrete criterion for measuring progress, recorded by the patient routinely and reviewed by the physician on follow up visits, making it easier to monitor. At the same time, the

patient stays on track, reaches the target dates with a sense of achievement and motivation. Here, questions like, how much/ how many, how often (should progress be assessed), the parameters for success/ failure are to be answered. For instance, if the target is to walk briskly for 30 minutes, the monitors would be distance covered or steps walked or calories burnt per day, reduction in abdominal circumference/ weight (as a biweekly monitor). Modern technologies like apps to count step and calories burnt, are easily accessible, feasible and can be used for easy supervision. ATTAINABLE makes sure that the target is challenging, yet achievable. It addresses the problems or hurdles that the patient may face while completing the task and the steps to be taken to avoid or solve them. For a target of 30 minutes brisk walk per day, patient has to start small with 15-20 minutes, increasing it gradually till the target is reached. This will reduce the chances of failure. Group exercises usually fetch better results. RELEVANT and REALISTIC assess whether the goal is in sync with the long-term plan and if it is worthwhile. Patient should not be expected to exercise for one week and lose 3 kilograms, nor should the patient aim to shed all extra body fat at once. Last but not the least, a TIME BOUND goal, makes sure that the goal is attainable over a short period of time. It creates a sense of urgency and better time management. It answers questions like what can the patient do 6 months from now? what can he/she do 6 weeks from now? what can he/she do today? A goal suggesting the patient to exercise everyday will have much less effect than a goal of walking for 30 minutes by the end of 3 weeks. Exercise requirement varies from person to person, similar to what is observed with the drugs given.

When applied to our study group, we found a significant reduction in random blood sugar in 44 patients out of 52 and a reduced A1C level in 47 patients.

Though the decrement in the latter was not statistically significant, yet a noteworthy improvement in compliance to exercise regimen, healthy lifestyle and regular follow up was noted.

The trial, albeit small, opens up a momentous horizon of opportunities in terms of research and therapeutics. Successful management of the disease
with minimal drugs and maximum lifestyle intervention will not only aid the patient financially, a simultaneously improved quality of life maybe expected. In a disease that has no permanent cure yet, every small step like this is of paramount importance.

**Conclusion**

An alternate approach to prescribing exercise and its utility was analysed objectively by doing a prospective follow up single centred study. It showed a reduction in blood sugar and A1C levels after a period of three months. Additional benefits of better follow up, reduced financial burden, increased compliance to the said regimen were observed.

Though large multicentric meta analyses would be beneficial for more reliable results, its is safe to say that it’s time to be SMART and tap into the highly promising role of exercise as a therapeutic device to tackle diabetes.

**References**

Insulin resistance at adipose tissue in pathogenesis of diabetes mellitus. Adipose tissue is also very important in impair insulin secretory capacity and worsen insulin resistance and further of postprandial hyperglycaemia, may production, it leads into aggravation failure to suppress endogenous glucose production. These mechanisms are responsible for progression of diabetes mellitus and also these are the targets for pharmacological therapy. Initially diet and lifestyle modification is advocated with monotherapy which is mostly metformin unless there is a contraindication for its use. Monotherapy may assist patients in achieving a target of HbA1c less than 7%.

However, with progression of disease, in most instances monotherapy loses its efficacy over time as evident by the continued increase in HbA1c. In the presence of high mean baseline HbA1c of 8.2–8.4%, glycaemic control was achieved by only 25% diabetic patients with metformin monotherapy. Combination therapy with established medications is frequently used when adequate glycaemic control has not been achieved with monotherapy. UKPDS reported by three years, half of the patients required combination therapy, and by nine years, 75% patients needed combination therapy.

**Evogliptin**

Evogliptin is a new molecule containing a β-amino acid structure that was originally developed by Dong-A ST Co., Ltd. Evogliptin demonstrated superior potency, safety and durability in nonclinical studies; has 10 times higher potency in DPP4 inhibition than Sitagliptin; is highly selective to DPP4; has favourable pharmacokinetic properties, such as a high oral bioavailability and rapid distribution into tissues; and has a relatively low urinary excretion rate than Sitagliptin. Evogliptin showed to have a wide safety margin in safety pharmacological studies, chronic toxicology studies, and carcinogenicity studies, and toxicology studies, and carcinogenicity studies.

**Introduction**

Type 2 Diabetes Mellitus (T2DM) is a progressive disorder, which is characterized by impaired insulin sensitivity, reduced insulin secretion and progressive failure of β-cells. The second highest number of people with diabetes in the world currently is in India (77.0 million) and these numbers are expected to increase to 101.0 million by 2030. The consequences of failure to suppress endogenous glucose production, it leads into aggravation of postprandial hyperglycaemia, may worsen insulin resistance and further impair insulin secretory capacity. Adipose tissue is also very important in pathogenesis of diabetes mellitus. Insulin resistance at adipose tissue leads to increased lipolysis, leading to increased free fatty acids in blood.

In T2DM addition to insulin resistance, β-cell dysfunction plays a major role in the progression of disease. As demonstrated by the UK Prospective Diabetes Study (UKPDS), patients with T2DM had only 60% of their predicted β-cell function as measured by the homeostatic model assessment (HOMA); furthermore, the β-cell function declined to 25% after 6 years.

Therefore, T2DM results from defects in multiple organ sites, insulin resistance, impaired pancreatic insulin secretion and increased hepatic glucose production. These mechanisms are responsible for progression of diabetes mellitus and also these are the targets for pharmacological therapy. Initially diet and lifestyle modification is advocated with monotherapy which is mostly metformin unless there is a contraindication for its use. Monotherapy may assist patients in achieving a target of HbA1c less than 7%.

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studies, relative to the exposure in humans. Evogliptin has been studied in two Phase III RCTs in South Korean patients with Type 2 DM, it has a low potential for interaction with other co-administered drugs. Evogliptin is approved in South Korea as well as in India by Drug Controller General of India (DCGI), for the treatment of type-2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control, as a monotherapy or in combination with Metformin.

Need for Combination therapy in diabetes mellitus

Importance of glycaemic control

The ADA’s ‘Standards of Medical Care in Diabetes’ guidelines 2020 recommends lowering HbA1c to <7.0% or <53 mmol/mol in most patients to reduce the incidence of microvascular disease. Although early initiation of insulin treatment remains an option for management of diabetic patients who cannot achieve euglycemia on oral hypoglycemic agents, higher costs and lower patient acceptability (due to fear of injections) remain significant disadvantages of such therapy. On both accounts, oral hypoglycemic drugs score better. A combination of drugs with different mechanisms of action may be the answer to treat complex disease like diabetes with the ever-elusive aim to achieve euglycemia. The most popular combinations are metformin with either sulfonylurea or DPP4 Inhibitors. Combination therapy with two antidiabetic molecules has been shown to lower HbA1c levels by an additional 0.5–1.0%. In addition, the selected regimen should ideally exert a physiologically rapid prandial insulin response with minimal side effects such as hypoglycemia and weight gain. It is also important for the combination therapy to be at least additive and possibly synergistic in their mechanisms of action.

Rationale for using combination drug therapy

Type-2 diabetes mellitus can be initially treated with monotherapy using oral glucose-lowering drugs but often requires the addition of another oral hypoglycaemic agents, due to the heterogeneity of this condition. Hence, a combination therapy, targeting one or more pathophysiological pathways for synergistic effect would facilitate in reaching glycaemic goal. Analysis from the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that after 3 years of longitudinal follow up, only 50% of the initial cohort could achieve the target HbA1c control of <7% while the remaining 50% required the addition of a second drug for diabetes control. By the time of nine years, 75% of subjects required multiple therapies to achieve the target HbA1c control. American Diabetes Association, 2020 have also suggested that if treatment with monotherapy does not result in optimal blood glucose levels then dual therapy should be initiated.

To overcome high failure rate of long-term monotherapy and progression of vascular complications developed due to postprandial glucose excursions, a combined therapy of oral antidiabetic agents with complementary modes of action should be considered. Studies have proved that a combination therapy with two or three therapeutic agents that target different facets of glucose metabolism (e.g. insulin resistance and defects in insulin secretion) can elicit better glycaemic control and lower HbA1c levels by an additional 0.5–1.0%.

The co-administration of a DPP-4 inhibitor and metformin comprises an effective treatment for T2DM due to their complementary mechanisms of action. DPP-4 inhibitor combined with metformin resulted in increased glycaemic control in subjects with T2DM who exhibited inadequate improvement in glycaemic control with metformin alone.

Evogliptin combination with Metformin

For over 50 years, metformin has been the most common first-line treatment for T2DM worldwide. Metformin primarily reduces hepatic glucose production, intestinal glucose absorption, and increase insulin sensitivity (improved peripheral glucose uptake and utilization). This effect increases insulin sensitivity in subjects with insulin resistance. Evolving evidence suggests that treatment with metformin is associated with reduction in all-cause mortality, even in overweight subjects with T2DM.

Evogliptin is a newly developed DPP-4 inhibitor for the treatment of T2DM, which increases GLP-1 and GIP, thus inhibits glucagon release, which in turn increases insulin secretion, decreasing gastric emptying, and thereby controlling blood glucose levels. In a first-in-human study, Evogliptin was well tolerated and showed dose proportional pharmacokinetics (doses between 1.25 and 60 mg) with a long half-life (30 hours) after a single administration. In terms of efficacy, monotherapy with Evogliptin (5 mg dose daily for 12 weeks) significantly reduced the mean HbA1c by 0.66%, and improved oral glucose tolerance test (OGTT) results and β-cell function compared to the placebo in subjects with type 2 DM who exhibited inadequate glycaemic control with diet and exercise alone.

Once daily dose of evogliptin (5 mg) was approved in the Republic of Korea (October 2015) and in India by DCGI (August 2019) for treatment of type-2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control, when used as a mono therapy or in combination with Metformin.

FDC of Evogliptin and Metformin Hydrochloride Extended Release Tablets (2.5/500mg, 2.5/850 mg, and 5/1000 mg) was approved by Korea in May 2016 under the product name of Sugamet® XR Tab. In India, DCGI is also approved FDC of Evogliptin and Metformin hydrochloride sustained release tablet (5 mg/500mg SR and 5/1000 mg SR).

Evogliptin is expected to be used as the add-on agent to metformin; therefore, the fixed-dose combination (FDC) formulation of evogliptin and metformin might increase therapeutic success by improving medication adherence compared with taking two individual component tablets. Indeed, the use of FDC formulations of two or more therapeutic agents with complementary mechanisms of action has been increasing in the clinical setting, and studies have shown that FDCs are more effective than concomitant administration of individual components.

Efficacy

Hong SM et al conducted an RCT in native Koreans in 222 subjects with HbA1c levels of 6.5% to 11% who were receiving stable doses of Metformin (≥1000 mg/dL). Subjects were randomized 1:1 to receive add-on Evogliptin 5 mg (N = 112) or Sitagliptin...
Table 1: Summary of efficacy results

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Study author</th>
<th>Number of subjects</th>
<th>Study design</th>
<th>Results</th>
<th>Ref No.</th>
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<tr>
<td>1</td>
<td>Hong SM et al</td>
<td>222 patients</td>
<td>24-week RCT</td>
<td>Mean changes in HbA1c of Evogliptin or Sitagliptin were −0.59% and −0.65%, respectively. The between-group difference was 0.06% (2-sided 95% confidence interval, −0.10 to 0.22), demonstrating non-inferiority.</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>Ajmani AK et al</td>
<td>184 patients</td>
<td>24-week randomized, double-blind, non-inferiority</td>
<td>After 12 weeks of treatment a significant reduction in HbA1c was observed in both groups (Evogliptin: −0.37±0.16; Sitagliptin: −0.32±0.14; p&lt;0.05 for both); the results were comparable between the groups (p = 0.783). At 24 weeks, a further reduction in HbA1c was observed in each treatment arm (Evogliptin, −0.55±0.19; Sitagliptin, −0.48±0.21; p&lt;0.001 for both groups); however, the results were statistically insignificant.</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>Babenko AY et al</td>
<td>320 patients</td>
<td>2 weeks screening plus 24 weeks treatment</td>
<td>Mean ± standard deviation of decrease in HbA1c in Evogliptin arm was 0.58±0.70 and Sitagliptin arm was 0.61±0.66 (both p &lt; 0.0001). In the group difference in the HbA1c at 24 weeks, the mean value 0.03%[95% CI: −0.14; 0.19%]</td>
<td>17</td>
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**Fig. 1: Mean change in HbA1c Hong SM et al study**

<table>
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<tr>
<th>HbA1c (%)</th>
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<td>Study arm</td>
<td>Evogliptin 5 mg</td>
<td>Siteglptin 100 mg</td>
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</tbody>
</table>

**Fig. 2: Mean change in HbA1c in Indian trial Ajmani AK et al study**

100 mg (N = 110) once daily for 24 weeks.

Mean changes in HbA1c following addition of Evogliptin or Sitagliptin were −0.59% and −0.65%, respectively. The between-group difference was 0.06% (2-sided 95% confidence interval, −0.10 to 0.22), demonstrating non-inferiority. After the 52-week treatment, subjects receiving Evogliptin had a persistently decreased level of HbA1c (−0.44% ±0.65%, p<.0001). Evogliptin and Sitagliptin decreased FPG (-0.60±1.11 mmol/L and 0.59±1.47 mmol/L, respectively; all p < .0001) levels from baseline through week 24 with no statistically significant difference between the two groups (p = 0.7155).

Owing to ethnic difference between the Korean and Indian population, Alkem laboratories conducted a similar study in Indian population. Ajmani AK et al conducted a clinical trial in 184 T2DM Indian subjects with uncontrolled diabetes (HbA1c >7%-10%) after ≥8 weeks of a stable dose (>1 g/day) of Metformin monotherapy. Subjects were randomized to receive add-on Evogliptin 5 mg or Sitagliptin 100 mg for 24 weeks. Mean baseline HbA1c level was 8.34%±0.75% in the overall per-protocol population and similar between the two treatment groups (Evogliptin 8.33±0.82%; Sitagliptin 8.35±0.67%; p=0.905). After 12 weeks of treatment a significant reduction in HbA1c was observed in both groups (Evogliptin -0.37±0.16%; Sitagliptin -0.32±0.14%; p<0.05 for both); the results were comparable between the groups (p=0.783). At 24 weeks, a further reduction in HbA1c was observed in each treatment arm (Evogliptin, −0.55±0.19%; Sitagliptin, −0.48±0.21%; p<0.001 for both groups); however, the results were statistically insignificant.

The mean FPG level at baseline was numerically higher in the Sitagliptin group (Evogliptin, 162.13±60.82 mg/dL vs. Sitagliptin, 174.54±62.22 mg/dL). However, the reductions in FPG were similar with Evogliptin and Sitagliptin at 12 weeks (-19.08±71.23 mg/dL vs. 24.74±77.42 mg/dL; p = 0.360) and at 24 weeks (-22.96±67.01 mg/dL vs. −33.58±79.73 mg/dL; p = 0.906). Babenko et al showed that the primary endpoint compared to baseline, HbA1c (%) changed after 24 weeks of treatment. The mean ± standard
deviation of Evogliptin arm was 0.58 ± 0.70 and Sitagliptin arm was −0.61 ± 0.66 (both p < 0.0001).

At 24 weeks, the mean values changed for HbA1c was 0.03% [95% CI: −0.14; 0.19%].

**Safety**

Hong SM et al15 demonstrated, both treatments were well tolerated, with incidences and types of adverse events comparable between the two groups. Hypoglycaemic events, mostly mild, were reported in 0.9% of subjects treated with evogliptin and in 2.8% of subjects treated with sitagliptin for 24 weeks.

Ajmani AK et al16 demonstrated, treatment-emergent adverse events, reported in 52 subjects (n [%]: Evogliptin, 23 [25]; Sitagliptin, 29 [31.5%]), were generally mild; most common being dyslipidaemia, reported in 11 (6%) subjects.

Babenko et al17 showed that both treatment was well tolerated and there were no serious adverse drug reaction noted.

Overall result from all three trials gastrointestinal tach related side effects i.e. dyspepsia, headache, musculoskeletal related pain and nasopharyngitis were noted in evogliptin and sitagliptin groups.15-17

**Discussion**

In spite of the availability of many different oral agents for the management of T2DM, almost half of individuals remain inadequately controlled. Accessibility to effective and tolerable combination therapy may permit more patients to achieve therapeutic goals. Numerous studies have confirmed that combining oral antidiabetic agents from different classes are more effective in glucose lowering than maximal doses of a single drug. Usage of metformin therapy as a first line, at the time of diabetes diagnosis with rapid intensification of subsequent drug therapy has been suggested by both the European Association for the Study of Diabetes and American Diabetes Association.18 Many multicentric, randomized, double-blinded, placebo-controlled trials have shown that adding DPP-4 inhibitors to metformin provide a greater reduction in glycated hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) than adding placebo to metformin monotherapy-treated patients with inadequately controlled T2DM. Evogliptin, a novel potent and selective DPP-4 inhibitor, has established glucose-lowering efficacy in both preclinical and clinical studies.19 In 2015, Evogliptin received the first global approval in South Korea for use in T2DM patients inadequately controlled by diet and exercise as well as for those with uncontrolled T2DM on metformin monotherapy and was subsequently also approved in India in August 2018.16 FDC of Evogliptin and sustained release metformin is already available in South Korea and is recently approved in India. In India it is available as a FDC of Evogliptin 5mg plus Metformin 500 mg / 1000 mg in sustain release form for the treatment of T2DM.

Evogliptin is approved for treatment of type-2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control, when used as a mono therapy or in combination with Metformin; thus the fixed-dose combination (FDC) of Evogliptin and Metformin might increase therapeutic success by improving medication adherence compared with taking two individual component tablets. The co-administration of Evogliptin and metformin showed no clinically relevant pharmacokinetic differences.
compared to the administration of each drug alone. The co-administered metformin did not alter the inhibitory effect of Evogliptin on DPP-4 activity. In fact, the synergistic actions of Evogliptin and metformin, which increase active GLP-1 and decrease glucose, showed additive effects. Complementary combination therapy with Evogliptin and Metformin lowers glucose by augmentation of insulin secretion, suppression of glucagon secretion, and insulin sensitization. Use of this combination in diabetes management will provide a superior degree of HbA1c lowering than that seen with the use of either drug as monotherapy, is unlikely to cause significant hypoglycemia, and is generally not associated with weight gain. The effectiveness and tolerability associated with the use of Evogliptin and metformin combination therapy makes this an attractive option in diabetes management. Efficacy and safety of Evogliptin and Metformin has been well established in various multicentric randomized clinical trials of Evogliptin–metformin have demonstrated decreases in HbA1c ranging from 0.5% to 0.6%, with a significantly higher proportion of subjects lowering their HbA1c to less than 7%.

Conclusion

Evogliptin and metformin exert a complementary glucose-lowering effect and represent a well-tolerated option for patients requiring therapy for type 2 diabetes. This combination should play an important role in the current treatment algorithm for this condition.

Acknowledgements

Authors are thankful to Dr Suraj Ghag and Dr Ashish Zalke for their contribution.

Conflict of interest

Dr Akhilesh D Sharma, Dr Abhijit A Trailokya, Dr Amol Aiwale, Dr Suraj Ghag and Dr Ashish Zalke are associated with Alkem Lab. Mumbai.

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2. Moses RG. Combination Therapy for Patients with Type 2 Diabetes: Repaglinide in Combination with Metformin, Expert Rev Endocrinol Metab 2010; 5:331–342.
4. Dong-A ST. Investigator’s Brochure. Evogliptin Tablets for the Treatment of Type II DM. Version 4.0. Date issued: November 22, 2017
Diabetic Foot Care Knowledge and Practices in Rural North India: Insights for Preventive Podiatry

Madhur Verma1,2, Nikita Sharma3, Rashi2, Varun Arora3, Bashar MA2, Bhola Nath1, Sanjay Kalra4

Abstract

Backgrounds: Diabetic foot ulcer (DFU) is one of the most dreaded complications of Type 2 Diabetes Mellitus (T2DM). Preventive podiatry is most efficient way of minimising DFU. The main aim of the study was to assess the knowledge and foot care practices among patients living with T2DM concerning the DFU.

Methods: We conducted a cross-sectional study in a rural-area of Haryana, India between January to March 2019 amongst 416 people living with T2DM after using multistage random sampling. A pre-tested, structured survey instrument prepared from the recommendation of the American College of Foot and Ankle Surgeons and the Diabetes UK was used after Hindi translation as per standard protocol. The knowledge and practices were classified as good, satisfactory and poor if the total score was between 8–11, 6–7 and <6.

Results: 14.2% had a previous history of DFU. The prevalence of good, satisfactory and poor knowledge was 63.5%, 12.5% and 24.0%. Further, 46.7%, 32.7% and 20.6% respondents depicted good, satisfactory and poor practices regarding foot care. On multivariate binary logistic regression analysis, younger age group, higher education, Per capita family income in INR, Blood glucose levels, HbA1c Levels, physical activity and previous history of DFU emerged as significant predictors of good foot-care knowledge and practices.

Conclusion: There is an evident gap between foot-care knowledge and practices that should be addressed through comprehensive behaviour change strategies. Comprehensive risk-assessments for diabetes associated complications needs to be piloted at community level to assess the feasibility.

Introduction

Type 2 diabetes mellitus (T2DM) is presently afflicting 463 million people worldwide and is estimated to rapidly increase to 578 million people in 2030 as a consequence of longer life expectancy, sedentary lifestyle and changing dietary patterns.1,2 The current prevalence of T2DM in India is 8.9% (7.3–11.2) with approximately 77 million people living with T2DM in 2019. This number is estimated to escalate to about 134.2 million by 2045. India is also home to the second highest proportion (57%; 43.9 million) of undiagnosed T2DM cases.1

This rise in prevalence of T2DM is likely to bring a concomitant increase in its complications. Foot problems are amongst the important complications of T2DM, and they have emerged as a public health problem. Previous literature from both developed and developing countries have depicted the prevalence of diabetic foot ulcer (DFU) that ranges between 1.0% to 20%.3–7 DFU are a leading cause of admission, amputation and mortality in people living with T2DM. In addition, DFU also have substantial economic consequences, beside the direct costs of foot complications, there are also indirect costs relating to loss of productivity, individual patients’ and family costs and loss of health-related quality of life.8

People with diabetes are prone to develop DFU and with its other lower extremity clinical abnormalities if they do not have sound knowledge about it. Therefore, increasing the knowledge, awareness and self-care practices of the foot among people living with T2DM is seen as a cost effective way of preventing DFU especially in resource constrained countries like India.9,10 There are very few studies on knowledge and practice of foot care among people living with T2DM from India. Therefore, the present study aimed to assess the knowledge and foot care practices among people living with T2DM attending primary and secondary care centres. The specific objectives of the study were to assess the socio-demographic and clinical factors associated with DFU, the knowledge about foot care (prevention and management) and foot-care practices being followed by such people living with T2DM in rural area of Haryana, North India.

Methods

Study period: the study was conducted over a period of 3 months i.e. from Jan to March, 2019.

Study design: A cross-sectional study design was used.

Study settings: Dighal Block in the district Jhajhar of Haryana, India was selected for this study. It is the field practice area of Post Graduate Institute of Medical Sciences in Rohtak district. The area has a Community Health Centre that caters to a population of 1,09,913 with 5 Primary Health Centres (PHCs) and 20 Sub Centres (SCs).

Study population

National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and
Stroke (NPCDCS) is being actively implemented in the study area and hence record is maintained pertaining to adults who are living with T2DM. The same records were used to identify the study population. The study participants included ambulatory adult patients (>30 years) living with T2DM for a period of more than 1 year. Patients having cognitive impairment/hearing problem were excluded from the study.

### Sample size and sampling

The sample size was calculated by using an online sample size calculator (Open Epi, Version 3.01) available in public domain from: https://www.openepi.com/Menu/ OE_Menu.htm. Considering prevalence of DFU in T2DM as 15%, the minimum required sample size was calculated to be 392, with a 95% confidence interval, a 5% type-I error rate. The test power was considered as 80 and the effect size was assigned a value of 2.0. After rounding off the figures, the total sample size included 400 people living with T2DM that were to be invited to take part in the study. After speculating a 5% for non-response from each village, the final sample was taken as 420. Multi-stage random sampling method was chosen for sampling. Firstly, two PHCs out of the five PHCs were randomly selected. Then two villages under each PHC were selected. While selecting representative sample of villages under each PHC, it was decided to choose one village having a population above 5000 from each PHC and one village at a distance beyond 5 km from PHC. Then, in the third stage, people with T2DM were enlisted from the NPCDCS registers, from which desired sample size was chosen randomly to give us the final sample size.

### Date variables and data collection procedures

Data were collected with the help of a semi-structured tool by the medical (MBBS) interns by face to face interviews with the respondents. These interns were posted at the rural health-centres, and they were first given necessary training regarding diabetes self-care practices including foot care practices by the one of co-investigators working as their in-charge. The tool consisted of two parts. Part A included information pertaining to socio-demographic and clinical profile of the patients. Part B included pre-tested, structured survey instrument (11 questions each on foot care knowledge and current self-foot care practices respectively marked in a dichotomous fashion) prepared from the recommendation of the American College of Foot and Ankle Surgeons and the Diabetes UK and used in similar previous study was used.

The original questionnaire is in English, but was adapted, and translated to Hindi as per WHO standard protocol.

### Statistical analysis

The data was collected in and double-entered, validated and analysed using EpiData version 3.1 for entry and version 2.2.2.182 for analysis (EpiData Association, Odense, Denmark). Descriptive analysis was performed in the form of frequency and proportions for categorical variables. The response to questions on knowledge, and practices to foot care were analysed and scored appropriately. The scores were classified as good, satisfactory and poor if the total scores were ≥70 (8–11 correct answers), between 50–69 (6–7), or <50 (<6 correct answers). Chi square test was used to assess the significance of the responses. The predictors of knowledge and practices regarding the foot care were suggested using multivariable logistic regression analysis, for the this purpose, good and satisfactory results were merged to form one single variable and were compared with the poor score. Only the significant factors (p value <0.2 on univariable logistic regression analysis) were included to build the final model using the multivariable analysis. A p-value <0.05 was considered statistically significant.

### Table 1: Socio-demographic characteristics of the study participants living with diabetes as per the history of diabetic foot ulcers.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Previous history of diabetic foot ulcer</th>
<th>Chi-square (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (%)</td>
<td>No (%)</td>
</tr>
<tr>
<td>Total Participants</td>
<td>59 (14.2)</td>
<td>357 (85.8)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>23 (13.3)</td>
<td>150 (86.7)</td>
</tr>
<tr>
<td>Male</td>
<td>36 (14.8)</td>
<td>207 (85.2)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45 Years</td>
<td>4 (7.4)</td>
<td>50 (92.6)</td>
</tr>
<tr>
<td>45-60 Years</td>
<td>25 (14.5)</td>
<td>148 (85.5)</td>
</tr>
<tr>
<td>&gt;60 Years</td>
<td>30 (15.9)</td>
<td>159 (84.1)</td>
</tr>
<tr>
<td>BMI classification*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1 (2.3)</td>
<td>42 (97.7)</td>
</tr>
<tr>
<td>Overweight</td>
<td>9 (13.0)</td>
<td>60 (87.0)</td>
</tr>
<tr>
<td>Obese</td>
<td>49 (16.1)</td>
<td>255 (83.9)</td>
</tr>
<tr>
<td>Per capita family income in INR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1875</td>
<td>14 (15.1)</td>
<td>79 (84.9)</td>
</tr>
<tr>
<td>1876-6253</td>
<td>28 (12.8)</td>
<td>190 (87.2)</td>
</tr>
<tr>
<td>&gt;6254</td>
<td>17 (16.2)</td>
<td>88 (83.8)</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39 (15.2)</td>
<td>217 (84.8)</td>
</tr>
<tr>
<td>No</td>
<td>16 (16.0)</td>
<td>84 (84.0)</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 years</td>
<td>23 (13.3)</td>
<td>150 (86.7)</td>
</tr>
<tr>
<td>&gt;3 years</td>
<td>36 (14.8)</td>
<td>207 (85.2)</td>
</tr>
<tr>
<td>Type of treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Hypoglycemic Agents</td>
<td>47 (12.9)</td>
<td>316 (87.1)</td>
</tr>
<tr>
<td>Insulin</td>
<td>12 (35.3)</td>
<td>22 (64.7)</td>
</tr>
<tr>
<td>Only lifestyle modification</td>
<td>0</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Blood glucose levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>25 (17.0)</td>
<td>122 (83.0)</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>31 (12.4)</td>
<td>219 (87.6)</td>
</tr>
<tr>
<td>History of diabetes in family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37 (19.0)</td>
<td>158 (81.0)</td>
</tr>
<tr>
<td>No</td>
<td>22 (10.0)</td>
<td>199 (90.0)</td>
</tr>
<tr>
<td>Other comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35 (28.7)</td>
<td>87 (71.3)</td>
</tr>
<tr>
<td>No</td>
<td>24 (8.2)</td>
<td>270 (91.8)</td>
</tr>
</tbody>
</table>

*BMI classification as per modified Asian India Criteria; **Per capita income as per the modified BG Prasad Scale.
Ethical Clearance

Ethical Clearance was obtained from Pt. B. D. Sharma PGIMS, Rohtak (No. IEC/16/110; Dated 23rd, May, 2016). Written informed consent was obtained from all study participants before the interview. The consent form had two parts: information for the participant and the actual consent form, which were signed by the participant in the presence of a witness. Confidentiality was maintained and data is accessible only to the investigators.

Results

Characteristics of the study participants: A total of 416 persons with diabetes participated in the study. Overall, 59 (14.2%) of the participants had previous history of DFU. Table 1 depicts the socio-demographic and clinical profiles of the study participants. Previous history of DFU was significantly associated with being overweight or obese, type of treatment received, history of diabetes in family, and presence of other comorbidities, while no association was seen with age, gender, per-capita family income, occupation, and presence of other comorbidities depicted no association with either levels of knowledge or practices amongst the participant (data not tabulated).

Knowledge and practices regarding foot-care habits: About 63.5%, 12.5% and 24% participants living with T2DM reported good, satisfactory and poor knowledge regarding the DFU, while certain other factors like being overweight or obese, duration since diagnosis of diabetes, history of alcohol or tobacco usage, type of treatment, HbA1C levels, and presence of other comorbidities depicted no association with either levels of knowledge or practices amongst the participant (data not tabulated).

Factors affecting the knowledge and practices: Multivariable binary logistic regression analysis, depicted that younger age group, higher education, Per capita family income in INR, Blood glucose levels, HbA1c Levels, physical activity levels and previous history of DFU were associated with higher chances of having a good foot care knowledge. Similarly, higher education, adequate per capita income, higher physical activity and previous history of DFU emerged as significant predictors of good foot-care practices.

Table 2: Distribution of people living with type 2 diabetes mellitus as per their knowledge and practices regarding foot-care habits

<table>
<thead>
<tr>
<th>Knowledge</th>
<th>Poor</th>
<th>Satisfactory</th>
<th>Good</th>
<th>p-value</th>
<th>Poor</th>
<th>Satisfactory</th>
<th>Good</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>52 (12.5)</td>
<td>264</td>
<td>63.5</td>
<td>86</td>
<td>136 (32.7)</td>
<td>194</td>
<td>46.7</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46</td>
<td>26 (15.0)</td>
<td>101</td>
<td>58.4</td>
<td>39</td>
<td>51 (29.5)</td>
<td>83</td>
<td>46.0</td>
</tr>
<tr>
<td>Male</td>
<td>54</td>
<td>26 (10.7)</td>
<td>163</td>
<td>67.1</td>
<td>47</td>
<td>85 (35.0)</td>
<td>111</td>
<td>45.7</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;45 Years</td>
<td>1</td>
<td>11 (20.4)</td>
<td>42</td>
<td>77.8</td>
<td>3</td>
<td>19 (35.2)</td>
<td>32</td>
<td>59.3</td>
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<tr>
<td>45-60 Years</td>
<td>35</td>
<td>21 (12.1)</td>
<td>117</td>
<td>67.6</td>
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<td>57 (32.9)</td>
<td>87</td>
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<td>&gt;60 Years</td>
<td>64</td>
<td>20 (10.6)</td>
<td>105</td>
<td>55.6</td>
<td>54</td>
<td>60 (31.7)</td>
<td>75</td>
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<tr>
<td>Highest education</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Less than primary</td>
<td>79</td>
<td>24 (11.5)</td>
<td>106</td>
<td>50.7</td>
<td>69</td>
<td>33 (34.9)</td>
<td>67</td>
<td>32.1</td>
</tr>
<tr>
<td>Middle</td>
<td>9</td>
<td>3 (8.6)</td>
<td>23</td>
<td>65.7</td>
<td>10</td>
<td>12 (34.3)</td>
<td>13</td>
<td>37.1</td>
</tr>
<tr>
<td>Graduate</td>
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<td>78</td>
<td>85.7</td>
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<td>18 (19.8)</td>
<td>73</td>
<td>80.2</td>
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<td>7</td>
<td>17 (21.0)</td>
<td>57</td>
<td>70.4</td>
<td>7</td>
<td>33 (40.7)</td>
<td>41</td>
<td>50.6</td>
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<td>Occupation</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Professional</td>
<td>8</td>
<td>6 (9.5)</td>
<td>49</td>
<td>77.8</td>
<td>2</td>
<td>16 (25.4)</td>
<td>45</td>
<td>71.4</td>
</tr>
<tr>
<td>Farmers/ shop-owner</td>
<td>24</td>
<td>7 (6.8)</td>
<td>72</td>
<td>69.9</td>
<td>18</td>
<td>41 (39.8)</td>
<td>44</td>
<td>42.7</td>
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<tr>
<td>Semiskilled/unemployed</td>
<td>24</td>
<td>13 (5.3)</td>
<td>48</td>
<td>56.5</td>
<td>28</td>
<td>31 (36.5)</td>
<td>26</td>
<td>30.6</td>
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<tr>
<td>Homemaker</td>
<td>44</td>
<td>26 (15.8)</td>
<td>95</td>
<td>57.6</td>
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<td>49 (29.1)</td>
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<td>47.9</td>
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<tr>
<td>Per capita family income in INR</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1875</td>
<td>41</td>
<td>15 (16.1)</td>
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<td>39.8</td>
<td>36</td>
<td>38 (40.9)</td>
<td>19</td>
<td>20.4</td>
</tr>
<tr>
<td>1876-6253</td>
<td>51</td>
<td>27 (12.4)</td>
<td>140</td>
<td>64.2</td>
<td>10</td>
<td>16 (15.2)</td>
<td>79</td>
<td>75.2</td>
</tr>
<tr>
<td>&gt;6254</td>
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<td>10 (9.5)</td>
<td>87</td>
<td>82.9</td>
<td>40</td>
<td>82 (37.6)</td>
<td>96</td>
<td>44.0</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>35</td>
<td>31 (12.1)</td>
<td>190</td>
<td>74.2</td>
<td>38</td>
<td>71 (27.7)</td>
<td>147</td>
<td>57.4</td>
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<tr>
<td>No</td>
<td>48</td>
<td>11 (11.0)</td>
<td>41</td>
<td>41.0</td>
<td>36</td>
<td>37 (37.0)</td>
<td>27</td>
<td>27.0</td>
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<td>Blood glucose levels</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>23</td>
<td>18 (12.2)</td>
<td>106</td>
<td>72.1</td>
<td>22</td>
<td>48 (32.7)</td>
<td>77</td>
<td>52.4</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>74</td>
<td>32 (12.8)</td>
<td>144</td>
<td>57.6</td>
<td>61</td>
<td>81 (32.4)</td>
<td>108</td>
<td>43.2</td>
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<tr>
<td>History of diabetes in family</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>41</td>
<td>11 (5.6)</td>
<td>143</td>
<td>73.3</td>
<td>38</td>
<td>53 (27.2)</td>
<td>104</td>
<td>53.3</td>
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<tr>
<td>No</td>
<td>59</td>
<td>41 (18.6)</td>
<td>121</td>
<td>54.8</td>
<td>48</td>
<td>83 (37.6)</td>
<td>90</td>
<td>40.7</td>
</tr>
<tr>
<td>Previous history of diabetic foot ulcer</td>
<td>0.043</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9</td>
<td>4 (6.8)</td>
<td>46</td>
<td>78.0</td>
<td>7</td>
<td>13 (13.6)</td>
<td>44</td>
<td>47.4</td>
</tr>
<tr>
<td>No</td>
<td>91</td>
<td>48 (13.4)</td>
<td>218</td>
<td>61.1</td>
<td>79</td>
<td>22 (35.9)</td>
<td>150</td>
<td>42.0</td>
</tr>
</tbody>
</table>
Table 3: Factors affecting knowledge pertaining to foot care among adult participants living with Type 2 diabetes in rural area of Haryana

<table>
<thead>
<tr>
<th>Knowledge</th>
<th>Practices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted OR (95% C.I.)</td>
<td>p value</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;45 Years</td>
<td>10.95 (2.12-56.59)</td>
</tr>
<tr>
<td>45-60 Years</td>
<td>2.21 (1.08-4.54)</td>
</tr>
<tr>
<td>&gt;60 Years</td>
<td>Ref</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3.94 (0.51-30.33)</td>
</tr>
<tr>
<td>Male</td>
<td>Ref</td>
</tr>
<tr>
<td>Highest education</td>
<td></td>
</tr>
<tr>
<td>Less than primary</td>
<td>Ref</td>
</tr>
<tr>
<td>Middle</td>
<td>3.04 (1.15-8.04)</td>
</tr>
<tr>
<td>High school</td>
<td>8.86 (3.29-23.85)</td>
</tr>
<tr>
<td>Graduate</td>
<td>7.23 (1.97-26.49)</td>
</tr>
<tr>
<td>Per capita family income in INR</td>
<td></td>
</tr>
<tr>
<td>&lt;1875</td>
<td>Ref</td>
</tr>
<tr>
<td>1876-6253</td>
<td>0.40 (0.21-0.77)</td>
</tr>
<tr>
<td>&gt;6254</td>
<td>2.34 (0.94-5.80)</td>
</tr>
<tr>
<td>History of diabetes in family</td>
<td></td>
</tr>
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<td>No</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>1.31 (0.74-2.32)</td>
</tr>
<tr>
<td>HbA1c Levels</td>
<td></td>
</tr>
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<td>Not raised</td>
<td>Ref</td>
</tr>
<tr>
<td>Raised</td>
<td>0.32 (0.12-0.90)</td>
</tr>
<tr>
<td>NA</td>
<td>0.52 (0.17-1.57)</td>
</tr>
<tr>
<td>Blood glucose levels</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>Ref</td>
</tr>
<tr>
<td>Controlled</td>
<td>3.20 (1.65-6.21)</td>
</tr>
<tr>
<td>Physically Active</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>2.13 (1.59-3.67)</td>
</tr>
<tr>
<td>Prev. history of DFU*</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>2.72 (1.09-6.81)</td>
</tr>
</tbody>
</table>

*DFU: diabetic foot ulcer

(Table 3). Age and gender of the patient, severity of the disease as per the HbA1c levels, and history of diabetes in family were not observed to be significant predictors of knowledge or practices for DFU.

Discussion

There is a high prevalence of DFU in India. In our study about 14% persons with T2DM had past history of DFU. In Indian settings, the prevalence has been estimated between 3.5%-15%. There was a higher prevalence of DFU in obese and elderly population, similar to previous studies. Association between insulin treatment and DFU was similar to another study. We did not observe any significant association of DFU with factors like duration of T2DM, HbA1C levels, physical activity, hypertension, smoking and alcohol intake. Previous epidemiological studies have also reported mixed associations between DFU and Smoking, alcohol, HbA1C levels and physical activity. In our study, no difference in prevalence of DFU on the basis of gender and occupation suggests that farming should not be considered as an obvious cause of DFU in rural area. Anecdotally, in a high performing state like Haryana, respondents call themselves farmers, but on the contrary majority of the work is done by their laborers.

In our study more than half of the participants had good knowledge regarding foot care in T2DM unlike other studies where most of the participants had poor knowledge. The high prevalence of DFU is attributed to inadequate knowledge about the risk factors like the presence of Peripheral Vascular Diseases (PVD), invasive fungal infections, presence of callus, neuropathy, and poor socio-cultural practices like barefoot walking, use of improper footwear. Poor knowledge has been reported in elderly, low socio-economic classes and homemakers. Chances of having better knowledge regarding foot care were higher in younger age group (<45 years), high education status, abstinence from alcohol and past history of DFU.

In our study, less than half of the participants had good foot care practices despite having good knowledge. Many studies report have depicted similar trends. This indicates having good knowledge does not translate into good foot care practice. Association between poor foot care practices with old age and low education status has already been established in previous studies from India and Pakistan. Odds of foot care practices were high among young age, high school education and physical activity. Past history of DFU was strongly associated with both good foot care knowledge and practices. It has been observed that foot care practices improved among those who had received advice on foot care and those whose feet have been examined by a doctor at least once.

Our study has certain strengths which include a robust study design, with systematic multi-stage random sampling to have a representative sample. We used a comprehensive validated questionnaire that was translated in local language. We also acknowledge certain limitations in our study. First, this study was cross-sectional in nature, hence causality of DFU cannot be established. Second, the study has been conducted in a primarily agricultural rural area within a district. Hence, the study findings will be difficult to extrapolate to a non-agricultural and urban population. Third, we could not collect data pertaining to bare foot walking habits, use of foot wear, and drug adherence among the participants that would have helped us to answer few more pertinent questions.

The study has important implication in policy and clinic epidemiological practice. Our findings suggest the need for a greater primary prevention through education. There is a need to develop educational strategies based on three tier levels of prevention model. As per this model, we suggest use of primary education strategies for everybody who is living with T2DM to prevent DFU. Secondary education
strategies should target all those who have a positive history of DFU, and they should be educated to prevent the relapse of DFU incidents in future. Tertiary education strategies should aim to minimise the effects of DFU on the quality of life of such group of patients. High level of DFU in our study shows that we are grossly lacking in Primary education strategies, while significant association of education with Previous History of DFU (Table 2) suggests motivating results in pertaining to secondary education strategies. We can involve people living T2DM and a positive history of DFU for advocacy and health promotion sessions as motivation speakers. They can be requested to initiate the behaviour change communications with their peers living with T2DM as it is have a beneficial effect on community because of their larger societal acceptance. Formal self-care practices education module should be designed for patients living with T2DM with due emphasis to preventive diabetic. Generic education modules from the International Diabetes Federation can be modified after keeping in mind the current cultural and social factors and practices for effective advocacy against DFU.

To conclude, our community-based study has depicted high prevalence of DFU. There is an evident gap between foot care knowledge and practices that needs to be addressed through comprehensive behaviour change strategies. Comprehensive risk assessments for diabetic foot complications and foot care based on prevention, education and support needs to be piloted at community level to assess the feasibility.

Acknowledgement

We are thankful to the civil surgeon of Distt. Jhajjar, for giving us the permission to conduct the study. We are also thankful to the medical interns who selflessly helped us in data collection and promoting awareness regarding foot care practices amongst the people living with T2DM.

References

Evaluation of the Efficacy and Safety of Azilsartan in Adult Patients with Essential Hypertension: A Randomized, Phase-III Clinical Study in India

Shubhadeep Sinha1, Sreenivasa Chary1, Mohan Reddy Bandi1, Pankaj Thakur1*, Leela Talluri1, Vijay Kumar Reddy2, Manish Agarwal3, Sunil Naik K4, Azilsartan study in Indian Adult Patients of Essential Hypertension Investigators (AZILEHI) Group5

Abstract

Background: Globally, women and men over the age of 25 years suffer from hypertension, the need for new treatment strategies to treat hypertension is due to the multi-faceted nature of the disease. Lack of optimal blood pressure control can lead to multiple complications. Therefore, this phase 3 study was conducted to assess the efficacy, safety and tolerability of potential product azilsartan hydrochloride for reduction in blood pressure in Indian patients with essential hypertension.

Methods: This was a prospective, multicentre, randomized, comparative, parallel study of 303 participants over six weeks of treatment period with either azilsartan 40 mg or azilsartan 80 mg or telmisartan 40 mg in adult patients with essential hypertension. The primary endpoint was the change in mean trough sitting clinic systolic blood pressure (scSBP) from baseline to week 6. The secondary endpoints were the change in mean trough sitting clinic diastolic blood pressure (scDBP) from baseline and change in the 24-hour mean ambulatory systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline.

Results: The change in mean trough scSBP from baseline to week 6 was -27.2 ± 9.99, -28.2 ± 10.06 and -26.7 ± 9.72 (Per Patient (PP) Population) and -27.2 ± 9.93, -28.3 ± 10.01 and -26.7 ± 9.67 (Intent to Treat (ITT) Population) in the azilsartan 40mg, 80mg and telmisartan 40mg groups respectively. The lower limit of 95% CI of difference in mean systolic blood pressure was -2.35 (Azilsartan 40mg) and 1.32 (Azilsartan 80mg) is less than the non-inferiority margin (i.e. 2.67). The change in mean trough scDBP from baseline to week 6 was -13.1 ± 8.46, -12.9 ± 7.20, and -13.0 ± 7.92 (PP) and -13.1 ± 8.42, -12.9 ± 7.16 and -13.0 ± 7.92 (ITT) in Azilsartan 40 mg, Azilsartan 80 mg and Telmisartan 40 mg respectively. The reduction in trough scDBP in Azilsartan 40 mg (p=0.9461: PP; p=0.9330: ITT) and Azilsartan 80 mg (p=0.9090: PP; p=0.9158: ITT) was not statistically significant compared to Telmisartan 40 mg. The difference in fall in the trough scSBP, scDBP and ambulatory SBP and DBP was similar between the groups from baseline to week 6 (P >0.05). Headache and dizziness were the most frequent treatment-related adverse events.

Conclusion: Azilsartan is an effective blood pressure lowering drug and well tolerated and was non-inferior to telmisartan in its safety and efficacy.

Introduction

Essential hypertension is a common cardiovascular disorder with sustained systolic/diastolic blood pressure of ≥140/90 mmHg, according to Joint National committee (JNC VIII) on hypertension. The chronic elevated arterial pressure remains the major risk factor for heart disease, stroke, cardiac failure, renal insufficiency and dissecting aneurysm of aorta and its attendant complications like myocardial infarction and sudden cardiac death. Despite the availability of antihypertensive agents with various mechanisms of actions, only 13.8–32.5% of patients globally have adequately controlled hypertension (defined as <140/90 mm Hg), with significant disparities in awareness, treatment and control rates and opposite trends for those between high-income and low-to-mid-income countries.5 In India, 22.60% women and 23.10% men over the age of 25 years suffer from hypertension.4

Angiotensin II appears to exert a central role in both the pathophysiology of essential hypertension and arteriosclerosis-associated hypertension and insulin resistance. Azilsartan medoxomil, the 8th angiotensin receptor blocker (ARB) approved by USFDA in 2011 is a potent, long-acting, selective angiotensin II (AT1) receptor blocker for the treatment of hypertension, alone or in combination with other antihypertensive agents.7,8,9,10 It was discovered by modifying the tetrazole ring present in candesartan.11 It is a prodrug, that is quickly hydrolyzes into azilsartan in both the gastrointestinal tract and plasma, with estimated bio-

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Received: 02.01.2020; Revised: 06.10.2020; Accepted: 15.11.2020
Efficacy and safety endpoints

The primary efficacy endpoint was the change from baseline to week 6 in trough scSBP. Secondary endpoints included changes from baseline to week 6 in trough scDBP, 24-hour mean SBP and DBP measured by ABPM. Safety variables included all treatment emergent clinical adverse events (TEAEs), vital signs, laboratory assessments and 12-lead electrocardiographic (ECG) findings.

Statistical Analyses

To confirm the non-inferiority of azilsartan to telmisartan, with 85% power at 5% level of significance, non-inferiority margin (6) of -10% of the control value, a sample size of 85 evaluable patients were required per group. Assuming a follow up loss of about 20%, 101 patients were needed in each arm. Efficacy and safety analyses were performed in PP population which consisted of randomized patients who received the study medication and completed study without any major protocol deviations and ITT population which consisted of randomized patients who received at least one dose of the study drug at baseline and at least one efficacy evaluation day available. All patients who received at least one dose of the study drug considered for the safety population.

All continuous demographic parameters were summarized using number, mean, median, standard deviation, range and quartiles. All categorical demographic parameters were summarized using number and percentages. The statistically significance for the mean change from baseline to subsequent visits was analysed using analysis of covariance (ANCOVA) with treatment as fixed effect and site number, baseline scSBP and scDBP values as covariates. The non-inferiority was accepted if the lower bound of one-sided 95% CI was less than the noninferiority margin 10% of control value. P value<0.05 was considered statistically significant. All statistical analysis was performed using SAS® (version 9.2 and 9.3) system software (SAS Institute Inc., USA). Adverse events were coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA Version 18).

Material and Methods

Ethics

The study was approved by Institutional Review Boards at each study centre, and was conducted in accordance with the ethical provisions set out in the Declaration of Helsinki (Brazil, October 2013), the International Conference on Harmonisation, Harmonised Tripartite Guideline for GCP (Good Clinical Practice E6 R1) and all applicable local laws and regulations. Prior to any study related screening procedures, written informed consent was obtained from each patient before enrolment in the study. The trial was registered with Clinical Trial Registry- India (CTRI/2014/08/004840) before enrolment of first patient in the study.

Study design

This multicentre, randomized, three arm, 6-week, phase 3 study was designed to evaluate the efficacy and safety of azilsartan 40 mg and azilsartan 80 mg in comparison with telmisartan 40 mg in Indian patients with mild to moderate essential hypertension. The study was conducted at 12 multi-specialty hospitals across India from August 2014 to July 2015. Patients included in the study were randomized in 1:1:1 ratio to receive either 20 of azilsartan medoxomil or 40 mg of azilsartan medoxomil, or 20 mg of telmisartan once daily for 2 weeks. At the end of the 2 weeks, patients were force-titrated to 40 or 80 mgs of azilsartan medoxomil, or 40 mg of telmisartan, once daily for an additional 4 weeks. Overall 98 patients in azilsartan 40 mg, 103 patients in azilsartan 80 mg and 102 patients in telmisartan 40 mg enrolled in the study. Total study duration per patient was 9-12 weeks which included (1) screening phase of - 2 weeks, washout of previous antihypertensive therapy 3 to 4 weeks and randomization -(visit 1) (2) treatment period of 6 weeks includes day 1 of treatment (visit 2); end of 2 weeks’ treatment (visit 3); end of 6 weeks’ treatment (visit 4).

Key Inclusion and Exclusion criteria

Men and women of ≥18 years of age with mild to moderate essential hypertension with clinic sitting SBP of 140-180 mm Hg, 24-hour mean ambulatory SBP of 130 - 170 mm Hg and clinic sitting DBP ≤114 mm Hg at baseline. Patients with baseline 24-hour ambulatory blood pressure monitor (ABPM) reading of insufficient quality; taking other antihypertensive agents within 30 days prior to randomization; history of hypersensitivity to ARBs; clinically relevant or hemodynamically unstable cardiovascular diseases within 6 months of prior enrolment; secondary hypertension of any aetiology; known or suspected unilateral or bilateral renal artery stenosis; severe renal dysfunction or disease (creatinine clearance <30 ml/min/1.73 m²) at screening; alanine aminotransferase 2.5 times the upper limit of normal (ULN), active liver disease, or jaundice: hyperkalaemia (as per central laboratory reference ranges); pregnant and lactating women were excluded from the study.

Table 1: Demography and Other Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Azilsartan 40mg (N=98)</th>
<th>Azilsartan 80mg (N=103)</th>
<th>Telmisartan 40mg (N=102)</th>
<th>Overall (N=303)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>53(54.08%)</td>
<td>45(43.69%)</td>
<td>47 (46.08%)</td>
<td>145(47.85%)</td>
<td>0.4716</td>
</tr>
<tr>
<td>Female</td>
<td>45(45.92%)</td>
<td>58(56.31%)</td>
<td>55 (53.92%)</td>
<td>158(52.15%)</td>
<td>0.7585</td>
</tr>
<tr>
<td>Age (years, Mean ± SD)</td>
<td>47 ± 10</td>
<td>49 ± 10</td>
<td>47 ± 10</td>
<td>48 ± 10</td>
<td>0.9651</td>
</tr>
<tr>
<td>Height (cm, Mean ± SD)</td>
<td>162.2 ±9.83</td>
<td>159.6 ±9.85</td>
<td>159.5 ± 10.48</td>
<td>160.4±10.10</td>
<td>0.0586</td>
</tr>
<tr>
<td>Weight (kg, Mean ± SD)</td>
<td>69.3±10.31</td>
<td>65.5±12.40</td>
<td>68.4±11.58</td>
<td>67.7±11.56</td>
<td>0.5681</td>
</tr>
<tr>
<td>BMI (kg/m², Mean ± SD)</td>
<td>26.5±4.48</td>
<td>25.7±4.42</td>
<td>27.0±4.56</td>
<td>26.4±4.50</td>
<td>0.4318</td>
</tr>
</tbody>
</table>

N = number of subjects in specified treatment; n = number of subjects at specified category; *p values for categorical variables are calculated with Chisquare test and for continuous variables p value are calculated with independent t-test.
Results

Patient disposition and demographics

Of the 346 patients screened, 303 patients were randomized in a 1:1:1 ratio to azilsartan 40 mg, azilsartan 80 mg or telmisartan 40 mg. Out of 303 patients, 276 patients completed the study and 27 patients withdrew from the study. Reasons for withdrawal were adverse experience (n=1), refused treatment (n=1) lost to follow-up (n=10), and withdrawal of consent for participation (n=15). Efficacy and safety analyses were performed in PP population (n=276) and ITT population (n=297). Demographic and baseline characteristics were similar across the 3 treatment groups (Table 1).

Efficacy evaluation

Primary analysis

In per protocol population, the mean scSBP prior to treatment was 151.1 mm Hg, 152.3 mm Hg, 151.6 mm Hg reduced to 137.0 mmHg, 138.1 mmHg, 138.8 mm Hg at week 2 and 123.9 mm Hg, 124.0 mm Hg, 124.9 mm Hg at week 6 in azilsartan 40 mg, azilsartan 80 mg and telmisartan 40 mg respectively after treatment. The mean scSBP was reduced by -14.1 mm Hg, -14.1 mm Hg, -12.9 mm Hg at the end of week 2 and -27.2 mm Hg, -28.2 mm Hg, -26.7 mm Hg by week 6 in azilsartan 40 mg, azilsartan 80 mg and telmisartan 40 mg respectively (Table 2).

In intent to treat population, the mean scSBP prior to treatment was 151.5 mm Hg, 152.5 mm Hg, 151.9 mm Hg reduced to 137.6 mm Hg, 138.8 mm Hg, 139.7 mm Hg at week 2 and 123.9 mm Hg, 124.1 mm Hg, 124.9 mm Hg at week 6 in azilsartan 40 mg, azilsartan 80 mg and telmisartan 40 mg respectively. The mean scSBP was reduced by -13.9 mm Hg, -13.7 mm Hg, -12.2 mm Hg at the end of week 2 and -27.2 mm Hg, -28.3 mm Hg, -26.7 mm Hg by week 6 in azilsartan 40 mg, azilsartan 80 mg and telmisartan 40 mg respectively (Table 2). The mean scSBP
at end of week 2 and week 6 has shown statistically significant reduction in all the treatment groups ($P < 0.0001$).

The lower limit of 95% CI (Table 2) of difference in change in mean scSBP from baseline to week 6 between azilsartan 40 mg vs telmisartan 40 mg and azilsartan 80 mg vs telmisartan 40 mg is less than the non-inferiority margin (10% of the reference value i.e. 2.67). This confirms that the reduction in scSBP for azilsartan 40 mg and 80 mg was non-inferior to telmisartan 40 mg.

### Secondary analyses

The change in mean scSBP at the end of week 6 (Table 2) was statistically significant in all the treatment groups ($p < 0.0001$). The difference in change in mean scSBP & scDBP was comparable between the azilsartan 40 mg, azilsartan 80 mg and telmisartan 40 mg after week 2 and week 6 of treatment ($p > 0.05$) (Figures 1 and 2).

The change in mean 24-hour ambulatory SBP at week 6 was -25.7 mm Hg, -26.8 mm Hg, -30.3 mm Hg in azilsartan 40 mg, azilsartan 80 mg and telmisartan 40 mg respectively. The change in mean 24-hour ambulatory DBP at week 6 was -16.1 mm Hg, -14.2 mm Hg, -20.1 mm Hg in azilsartan 40 mg, azilsartan 80 mg and telmisartan 40 mg respectively (Table 3).

### Safety evaluation

Overall, 63 patients reported 88 AEs during the study period. Among them, 18 (18.37%) patients in azilsartan 40 mg reported 25 AEs, 25 (24.27%) patients in azilsartan 80 mg and telmisartan 40 mg reported 36 AEs while 20 (19.61%) patients in telmisartan 40 mg reported 27 AEs. Out of 88 AEs, 78 AEs resolved completely. Except one AE in treatment telmisartan 40 mg which was severe (diabetes mellitus), all the AEs were mild to moderate in severity. The most frequent adverse events reported were headache and dizziness in all the groups. Laboratory AEs (increased serum creatinine, creatinine and potassium levels and decreased creatinine clearance, high BP, type II diabetes mellitus) were reported. No deaths or serious adverse events reported in the study. There were no clinical significant ECG or chest X-ray findings observed in this study compared to baseline.

### Discussion

In the present study both Azilsartan 40 mg and 80 mg were noninferior to telmisartan 40 mg in reducing scSBP and scDBP, and 24 hour mean ambulatory SBP and DBP. In addition, patients in the azilsartan 80 mg group has shown slightly better reduction in scSBP than azilsartan 40 mg and Telmisartan 40 mg, although not statistically significant. These results are comparable with the previously published studies. White et al.\textsuperscript{14} reported the change in mean SBP of -16.4 mm Hg with azilsartan 40 mg and -16.7 with azilsartan 80 mg after 6 weeks of therapy. In a similar study, Bonner et al.\textsuperscript{19} reported the change in mean BP of -20.6 mm Hg with azilsartan 40 mg and -21.2 mm Hg with azilsartan 80 mg after 24 weeks of therapy. In another study, the mean systolic BP reduced from 159.9 mmHg to 146.95 mmHg, 139.60 mmHg, 134.45 mmHg, 129.85 mmHg and 126.35 mmHg ($P < 0.001$) at 1st week, 2nd week, 3rd week 4th week and 5th week respectively with azilsartan 40 mg.\textsuperscript{16}

According to the World Health Organization (WHO), a high rate of undetected and untreated essential hypertension is a major medical concern and most common attributable cause of preventable death in developed and developing nations.\textsuperscript{4} Despite the availability of many drugs, hypertension remains inadequately controlled. After 15 years of the clinical introduction of Losartan, the FDA approved Takeda’s azilsartan medoxomil (AT1) receptor blocker as the 8th ARB for the treatment of hypertension.\textsuperscript{16} It functions as a selective blocker similar to Telmisartan, the comparator drug in the study. Although the efficacy and tolerability of antihypertensive drug therapy are not the only factors that play a role in hypertension control rates, they are likely among the most important. The present study confirms that azilsartan demonstrates a consistent safety profile and clinically meaningful reductions in blood pressure in Indian patients with hypertension, similar to other populations around the world.

### Conclusion

Our study results provide evidence for long-term stable BP improvements with non-inferior efficacy at the 40-mg and 80-mg dose level compared with telmisartan 40 mg with optimal safety and tolerability profile.

### Acknowledgement

This study was sponsored by Hetero Labs Limited, India and all the study related materials including study drugs were provided by Hetero Labs Limited, India. Authors would like to thank other investigators in AZILEHI group (Dr. I.S. Gambhir, Dr. Jitendra Patel, Dr. Sibnanada Datta) and all the study subjects for their valuable participation in this study.

### References

Study of Endothelial Dysfunction by Flow Mediated Vasodilation in Individuals with Asymptomatic Hyperuricemia

Vaibhav Shukla, Jalees Fatima, Ankit Raj Varshney, Prerit Joshi, Ruman Kugashiya

Abstract

Introduction: Asymptomatic hyperuricemia is a condition where the serum uric acid levels are elevated but the individual does not have any sign or symptoms of gout or renal stones. The relationship of hyperuricemia with hypertension, diabetes and chronic kidney disease is established. There are studies which show an association of hyperuricemia with endothelial dysfunction thus increasing the cardiovascular risk in these individuals. We therefore undertook this study to observe endothelial dysfunction in individuals of asymptomatic hyperuricemia.

Methodology: This was a case control study where 40 individuals with asymptomatic hyperuricemia and 40 age and sex matched healthy controls with normal serum uric acid levels were included. Endothelial function was studied by flow mediated vasodilation in the brachial artery.

Results: The mean age of cases was 45.03±16.44 years while that of control subjects was 44.70±14.31. There were 22 females and 18 males among the cases while there were 24 females and 16 males among the controls. The mean serum uric acid level in cases was 7.27±1.13 mg% while that of controls was 4.52±1.05 mg%. The FMD was 5.57±1.39% in cases while it was 7.73±1.56% in controls and this difference was statistically significant.

Conclusion: The present study showed that significant endothelial dysfunction is present in individuals of asymptomatic hyperuricemia in comparison to healthy age and sex matched controls.

Introduction

Uric acid is the end product of purine metabolism. Uric acid acts as an antioxidant when present in appropriate concentration while its high concentration changes its action to pro-oxidant, contributing to the cardiovascular disease development. In most of the studies hyperuricemia is defined as >7.0 mg/dL of serum uric acid in men and ≥5.7 mg/dL in women. The prevalence rate of hyperuricemia in the general population is estimated at 20-25%, but only 4-6% in premenopausal women.


Hyperuricemia predisposes the patients to gout and nephrolithiasis. However, not all the cases of hyperuricemia are asymptomatic. A number of cases of hyperuricemia present asymptotically. Asymptomatic hyperuricemia is defined as the condition where the serum urate concentration is elevated but no signs or symptoms of monosodium urate (MSU) crystal deposition disease, such as gout, or uric acid renal disease, have occurred. Hyperuricemia has been recognized as an independent determinant of hypertension, diabetes, and chronic kidney diseases too. Relationship of hypertension, diabetes, chronic kidney disease and other cardiovascular diseases with endothelial dysfunction is well-known.

Incidentally, hyperuricemia has been shown to be associated with endothelial dysfunction too. Even in an asymptomatic state, hyperuricemia seems to pose cardiovascular risk by disturbing the normal endothelial function. Although the contemporary clinical guidelines do not recommend any intervention in
asymptomatic hyperuricemia, however, identification of this condition and thereafer identification of the causes for hyperuricemia could help in prevention of associated causes. Recognition of endothelial dysfunction in asymptomatic hyperuricemic patients might help in recognition of cardiovascular risk and its probable causes, and thus will help in checking this risk at its budding state itself by adopting appropriate preventive strategies in accordance with the cause of hyperuricemia.

Hence, the present study was planned to study the endothelial dysfunction in asymptomatic hyperuricemia individuals using ultrasound guided flow mediated dilation.

Methodology

This was a case control study and included 40 individuals with asymptomatic hyperuricemia (without gout and nephrolithiasis) and 40 age and sex matched controls. The exclusion criteria included T2DM, hypertension, CAD, stroke, peripheral vascular disease, smokers, CKD patients and individuals on drugs that affect uric acid levels.

All subjects had their serum uric acid, fasting lipid profile, FandPP blood sugar, USG-KUB done.

Individuals who were to be assessed for endothelial function had to be in fasting state. During the examination patient was kept at rest in a quite air conditioned room in supine position. A longitudinal section of the brachial artery was analysed (medial epicondyle was used as anatomical landmark for the brachial artery). Essentially the probe was held in the same position during the scan, and consequently. After a baseline measurement of the brachial artery diameter, a sphygmomanometer cuff, which was placed above the transducer position, was inflated to 50 mm of Hg above the systolic pressure to produce the ischemia in the forearm. The sphygmomanometer cuff was deflated after 5 minutes and then the brachial artery diameter measurement was again done at the same level. Flow Mediated Vasodilation (FMD), which reflects endothelium dependent vasodilation, was calculated as the percentage increase in diameter from baseline to the maximum value which was obtained after cuff deflation.

\[
\text{FMD} \, (\%) = \frac{D2 - D1}{D1} \times 100
\]

where, 
D2 - Brachial artery diameter at 5 mins post deflation 
D1 - Base line brachial artery diameter

Results

40 individuals with asymptomatic hyperuricemia (cases) and 40 age, sex and BMI matched healthy controls were included in the study. The mean age of cases (Group I) was 45.03±16.44 years while that of control subjects (Group II) was 44.70±14.31. There were 22 females and 18 males among the cases while there were 24 females and 16 males among the controls. The mean serum uric acid level of cases was 7.27±1.13 mg% while that of controls was 4.52±1.05 mg%.

Subjects in both cases as well as controls had comparable systolic and diastolic blood pressures. Baseline brachial artery diameter of cases of asymptomatic hyperuricemia i.e. Group I (3.87±0.38 mm) was found to be higher as compared to healthy controls i.e. Group II (3.69±0.33 mm). Difference in baseline brachial diameter of above two groups was found to be significant statistically. Though post-deflation brachial artery diameter of Group I (3.87±0.38 mm) was higher than that of Group II (3.69±0.33 mm) but this difference was not found to be significant statistically.

A higher change in brachial artery diameter was observed among controls i.e. Group II (0.28±0.06 mm) as compared to cases of asymptomatic hyperuricemia (0.21±0.05 mm). Difference in change in brachial artery diameter of subjects of above two groups was found to be significant statistically.

Flow mediated dilation (FMD) of controls i.e. Group II (7.73±1.56%) was higher as compared to cases of hyperuricemia i.e. Group I (5.97±1.39%). Difference in FMD of cases and controls (Group I and Group II) was found to be significant statistically.

We also divided the cases into two groups based on the serum uric acid levels to see if there was any association between serum uric acid levels and FMD. We did not find any statistically significant relationship between serum uric acid levels and FMD.

Table 1: Height, weight and BMI of cases and controls

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I (n=40)</th>
<th>Group II (n=40)</th>
<th>Student 't' test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.53</td>
<td>8.92</td>
<td>161.40</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.55</td>
<td>14.07</td>
<td>66.63</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.42</td>
<td>5.40</td>
<td>25.28</td>
</tr>
</tbody>
</table>

Table 2: Serum uric acid values (mg%) in cases and controls

<table>
<thead>
<tr>
<th>Group</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=80)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases (n=40)</td>
<td>5.7</td>
<td>11.4</td>
<td>7.27</td>
<td>1.13</td>
</tr>
<tr>
<td>Controls (n=40)</td>
<td>2.2</td>
<td>6.6</td>
<td>4.52</td>
<td>1.05</td>
</tr>
<tr>
<td>Total (n=80)</td>
<td>2.2</td>
<td>11.4</td>
<td>5.90</td>
<td>1.05</td>
</tr>
</tbody>
</table>

't'=11.22; 'p'<0.001

Females (n=46)
Cases (n=22) 5.7 11.4 6.90 1.23
Controls (n=24) 2.3 5.6 4.33 0.77
Total (n=46) 2.3 11.4 5.56 1.64
't'=8.56; 'p'<0.001

Males (n=34)
Cases (n=28) 7.1 10.7 7.72 0.83
Controls (n=16) 2.2 6.6 4.81 1.35
Total (n=34) 2.2 10.7 6.35 1.83
't'=7.65; 'p'<0.001

Table 3: Brachial artery diameter and FMD values in cases and controls

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I (n=40)</th>
<th>Group II (n=40)</th>
<th>Student 't' test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Baseline brachial artery diameter</td>
<td>3.87</td>
<td>0.38</td>
<td>3.69</td>
</tr>
<tr>
<td>(in mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post deflation brachial artery</td>
<td>4.08</td>
<td>0.38</td>
<td>3.97</td>
</tr>
<tr>
<td>diameter (in mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in brachial artery diameter</td>
<td>0.21</td>
<td>0.05</td>
<td>0.28</td>
</tr>
<tr>
<td>(in mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMD (%)</td>
<td>5.57</td>
<td>1.39</td>
<td>7.73</td>
</tr>
</tbody>
</table>

Table 4: Association of Serum Uric acid and FMD among cases

<table>
<thead>
<tr>
<th>Uric acid level (mg/dl)</th>
<th>No. of cases</th>
<th>Min.</th>
<th>Max.</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Female cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.7-6.5</td>
<td>9</td>
<td>4.06</td>
<td>7.49</td>
<td>5.57</td>
<td>1.14</td>
</tr>
<tr>
<td>&gt;6.5</td>
<td>13</td>
<td>3.27</td>
<td>9.35</td>
<td>5.46</td>
<td>1.70</td>
</tr>
<tr>
<td>'t'=8.166; 'p'=0.870</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Male cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.1-8.0</td>
<td>14</td>
<td>3.95</td>
<td>7.21</td>
<td>5.55</td>
<td>1.08</td>
</tr>
<tr>
<td>&gt;8.0</td>
<td>4</td>
<td>3.92</td>
<td>8.35</td>
<td>6.07</td>
<td>2.14</td>
</tr>
<tr>
<td>'t'=6.888; 'p'=0.501</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Uric acid levels and FMD.
Hyperuricemia is considered to be a recognized risk factor for cardiovascular disease (CVD) including vascular disease, hypertension, metabolic syndrome and renal disease. Clinically, uric acid (UA) levels >7 mg/dl in males and >5.7 mg/dl in females are considered as hyperuricemia. Hyperuricemia shares the common risk factors as for cardiovascular disease such as alcohol consumption, intake of high fat diet and refined carbohydrate. Epidemiological studies have shown a cause-effect relationship between hyperuricemia and CVD. These studies have found that there is an association between high levels of UA and myocardial infarctions and cardiovascular death even after adjustment for related factors such as age, dyslipidemia and obesity. The increased cardiovascular risk through hyperuricemia is considered to be driven through induction of endothelial dysfunction. Experimental studies have shown that hyperuricemia results in a decrease of serum nitric oxide which in turn affects the endothelial functions.

Endothelial dysfunction not only is responsible for cardiovascular disease but it also affects the kidney function resulting into chronic kidney disease. It has been shown that higher serum uric acid level is associated with a significant rapid decline in eGFR and a higher risk of kidney failure, particularly in patients without proteinuria.

Interestingly, a lot of patients with hyperuricemia remain asymptomatic for a long duration. However, it is believed that in this latent phase, hyperuricemia induced endothelial dysfunction continues and is full-fledged reflected at an irreversible stage in terms of various cardiometabolic diseases as shown in longitudinal studies. Considering endothelial dysfunction as a surrogate marker of cardiometabolic disease risk and its relationship with hyperuricemia, the present study was carried out with an aim to study whether asymptomatic patients also experience endothelial dysfunction.

Ageing also has shown an effect on uric acid levels. Endothelial function is also affected by gender with females being more susceptible to endothelial dysfunction as compared to males. Uric acid levels are already known to have different cut-offs for males and females thus showing a gender discrepancy too. Given these relationships of endothelial dysfunction and uric acid levels with age and gender, the differences in age and gender profile of patients in different studies might be affected. However, to neutralize this effect almost all the studies have included a control group with matched age and gender in order to study the endothelial dysfunction in hyperuricemic individuals in relative terms. In present study too, we included an age- and gender-matched control group.

In present study, mean body mass index of cases was 25.42±4.50 kg/m², thus indicating that the cases tended to be in upper ranges of normal weight (18.5-25.0 kg/m²) or overweight (25.0-29.9 kg/m²) category. Similar to present study, a number of studies have reported the mean BMI of hyperuricemic subjects to be in overweight or obese category (>25 kg/m²). The association between uric acid levels and body mass index has been expressed in earlier studies too. Considering the fact that obesity is a recognized risk factor for cardiometabolic disorders, the relationship of uric acid, body mass index and endothelial dysfunction seems to be acting in unison towards increasing the cardiometabolic risk.

In the present study, baseline brachial artery diameter values in cases were found to be significantly higher as compared to controls, however, mean FMD values were found to be significantly lower in cases (5.57±1.39%) as compared to that in controls (7.73±1.56%), thus showing a significant difference between two groups and in turn proving the association of asymptomatic hyperuricemia with endothelial dysfunction.

An overview of several studies reveals significantly lower mean FMD values among asymptomatic hyperuricemia cases as compared to healthy controls. However, the proportional difference in present study is relatively lower (27.9%) as compared to a proportional difference ranging from 37.3% to 47.4%. One of the reasons for this could be relatively lower mean uric acid levels in control group. However, Kanbay et al. in their study reported this difference to be 15.3% which is even lower than the present study. The findings in turn suggest that hyperuricemic status does have a role on the endothelial function; however, its impact varies in different circumstances. For example, one of the studies showing highest intergroup differences (Zhen and Gui 2017) had subjects with high systolic blood pressure. As such, most of these studies being conducted in asymptomatic subjects have a limited information regarding the patient profile. Moreover, most of the studies have been conducted on small sample sizes. In one such study where complete patient profile was not available, DiGiosa et al. found mean FMD levels of 4.6±1% in asymptomatic hyperuricemic group as compared to 7.88±1.8% in healthy controls, thus showing a proportional FMD difference of 28.9%.

In fact, the association of endothelial dysfunction with hyperuricemia has also been shown in different studies evaluating symptomatic subjects. For instance, Mercuro et al. in a study of 32 hyperuricemic and 30 normouricemic patients with >20% cardiovascular disease risk found a proportional FMD difference of 48.2% between hyperuricemic and normouricemic subjects. In another study among psoriatic patients, Ibrahim et al. found a difference of 46.4% between normouricemic and hyperuricemic patients. Other workers also reported of a significant association between reduced endothelial function and hyperuricemia in different disease states.

In the present study, we could not find an association between uric acid levels and endothelial function when evaluated in categorical terms in males and females separately. The reason for this could be small sample size, particularly when divided into categorical classes. In view of the stated relationship between uric acid levels and endothelial function, the relationship needs to be evaluated in linear terms. While performing the linear correlations, we also evaluated the effect of other continuous variables such as age, body mass index, systolic and diastolic blood pressure too. The linear correlations were assessed, first in overall study population and then in cases and controls separately. Similarly, the same process was repeated for both the genders individually too. It was found that there was a mild
negative and significant correlation between uric acid levels and endothelial function (FMD) on overall evaluation. However, on evaluating it separately in cases and controls, no significant correlation between FMD and uric acid levels could be seen. On performing the correlation assessments individually for both the genders too, we also found same outcome. As far as performing the linear correlation is concerned, it is advisable to carry out the assessment in entire population in order to gauge the linearity of change in FMD levels corresponding to change in uric acid levels. Performing it separately in cases and controls restricts the linear evaluations in view of the narrow range of uric acid values in both the groups.

Similar to present study, Erdogan et al. 17 also found a weak negative correlation between uric acid levels and FMD values \((r=-0.255;\ p=0.004)\) which is similar to the trend obtained in present study. Ho et al. 24 also observed a near mild negative and significant correlation between uric acid levels and FMD \((r=-0.273;\ p=0.009)\) on combined evaluation as done in present study. Similar negative correlations between uric acid levels and FMD levels have also been observed by other workers.

The findings in present study thus highlight the effect of asymptomatic hyperuricemia on endothelium function. The findings in turn indicate a relationship between uric acid levels and cardio metabolic disorders. Unfortunately, the endothelial function has not been studied extensively in asymptomatic hyperuricemic patients anywhere in the world. There are only limited studies conducted on limited number of patients. Further studies on larger sample size at multiple centers will help in understanding this relationship in a better way.

**Conclusion**

The present study established that significant endothelial dysfunction is present in individuals with asymptomatic hyperuricemia and thus hyperuricemic status poses a greater risk of endothelial dysfunction and per se a greater risk of cardiometabolic disorders. Hence, uric acid levels should be considered as a surrogate marker for increased cardiovascular risk. Further studies on a larger sample size including those with longitudinal design are recommended to establish this relationship further.

**References**


Glycomet GP

Abridged Prescribing Information

**COMPOSITION:** Glycomet GP 0.5: Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 500 mg and glimepiride USP 1 mg. Glycomet GP 1: Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 850 mg and glimepiride USP 2 mg. Glycomet GP 2: Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 2 mg. Glycomet GP 2/850: Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 850 mg and glimepiride USP 1 mg. Glycomet GP 3/850: Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 1 mg. Glycomet GP 4/850: Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 2 mg. Glycomet GP 1 FORTE: Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 2 mg. Glycomet GP 2 FORTE: Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 2 mg. Glycomet GP 3 FORTE: Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 4 mg.

**INDICATIONS:** Glycomet GP is indicated for the management of patients with type 2 diabetes mellitus (T2DM) when diet, exercise and single agent (metformin hydrochloride or glimepiride alone) do not result in adequate glycemic control.

**DOSAGE AND ADMINISTRATION:** Dosage of Glycomet GP should be individualized on the basis of effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin hydrochloride 2,000 mg and glimepiride 3 mg. Initial dose: 1 tablet of Glycomet GP should be administered once daily during breakfast or the first main meal. Do not crush or chew the tablet. In severe cases the tablet may remain intact during transit through the gastrointestinal (GI) tract and will be eliminated intact as a whole. Patients should be advised to report to the nearest emergency ward if any component has already been released during transit.

**CONTRAINDICATIONS:** In patients hypersensitive to glimepiride, other sulfonylureas, other sulfonamides, metformin or any of the excipients of Glycomet GP; pregnancy and lactation; acute or chronic disease which may cause tissue hypoxia (myocardial infarction, shock, cardiac/respiratory failure) hepatic insufficiency, acute alcohol intoxication, alcoholism.

**WARNINGS:** Keep out of reach of children. Patient should be advised to report promptly exceptional stress situations (e.g. trauma, surgery, febrile infections) blood glucose regulation may deteriorate and a temporary change to insulin may be necessary to maintain good metabolic control. In case of lactic acidosis, patient should be hospitalized immediately.

**PRECAUTIONS:** In the initial weeks of treatment, the risk of hypoglycemia may be increased and necessitates especially careful monitoring. In patients with renal impairment, serum creatinine levels should be determined before initiating treatment and regularly thereafter: at least every three months. In patients with such study is planned, Glycomet GP should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and restarted only after renal function has been re-evaluated to ensure it is normal. Use of Glycomet GP should be discontinued 48 hours before any surgical procedure.

**ADVERSE REACTIONS:** For glimepiride - Hypoglycemia, temporary visual impairment; gastrointestinal symptoms like nausea, vomiting, abdominal pain, diarrhea may occur; occasional. For metformin – Gastrointestinal symptoms like nausea, vomiting, abdominal pain or discomfort may occur occasionally. For full prescribing information please write to: USV Limited, Arvind Vithal Gandhi Chowk, B.S. D. Marg, Govandi, Mumbai, Maharashtra – 400 088.

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1 Rosamond et al. (2009). Rosuvastatin 10mg & Rosuvastatin 20mg are lower priced in Indian market as per 1mg. Am J Cardiol 2019 May 15;123(10):1386-1397.

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*IMS MAT Dec 2018. # AIoCD MAT Jan 2020*
Impact of Thyroid Dysfunction on Insulin Resistance: A Study from a Tertiary Care Center in India

Swati Srivastava1*, Girish Mathur2, Gaurav Chauhan3, Priyanka Kapoor4, Prasun Bhaskar5, Gunja Jain6, Gurvi Chauhan7, Mukesh Chopra5

Abstract

Introduction: The thyroid hormones perpetuate a fine equilibrium of glucose metabolism. Abnormalities of thyroid function can disrupt this balance leading to glucose metabolism abnormalities and insulin resistance. Objectives: We studied the correlation between insulin resistance and thyroid status in hyperthyroid, euthyroid, and hypothyroid individuals. Methods: In this observational comparative analysis conducted at a tertiary care center, the 3 study groups comprised of 35 patients each with newly detected hyperthyroidism, hypothyroidism and euthyroid individuals. Assays were conducted for serum insulin, thyroid profile, blood sugar and routine biochemistry in the fasting state. The homeostasis model assessment for insulin resistance (HOMA-IR) was used to evaluate insulin resistance. Results: The mean HOMA-IR was highest in patients with hypothyroidism (3.22 ± 2.69) followed by the hyperthyroid group (2.25 ± 1.59). It was lowest in the euthyroid group (0.79 ± 0.58) with the intergroup difference being statistically significant (P<0.001). Hyperthyroid patients showed a significant positive correlation between TSH and HOMA-IR (r=0.945, P<0.001) whereas hyperthyroid patients showed positive correlation between FT3 and insulin resistance (r=0.706, P<0.001). Conclusion: Thyroid dysfunction is associated with an increase in insulin resistance and glucose abnormalities validating the resultant higher risk of related cardiovascular and metabolic abnormalities observed in these patients.

Introduction

The impact of thyroid hormones on glucose metabolism, basal energy expenditure and cardiovascular function has been documented. The cluster of high blood pressure, high triglycerides, central obesity and glucose metabolism abnormalities, similar to metabolic syndrome, signal the underlying pathophysiology involving insulin resistance.1

Studies evaluating association of thyroid dysfunction and insulin resistance have shown diverse results. Although some studies demonstrated insulin resistance in case with hypothyroidism, few did not show an association.4,5 Hyperthyroidism has previously been linked with insulin resistance in studies.6 Studies document that reduced insulin sensitivity may be related to increased occurrence of dyslipidemia and mild thyroid abnormalities in individuals suffering from type 2 diabetes mellitus.7 Thyroid hormone abnormalities disturb the fine balance of insulin sensitivity and lead to alterations of glucose metabolism. Thyroid disorders occur more frequently in patients suffering from diabetes mellitus with the prevalence being 13.4%. This is much higher than the prevalence in the general population.8 Thyroid hormone excess leads to glucose intolerance and sometimes precipitation of diabetic ketoacidosis. Hypothyroidism has been associated with episodes of hypoglycemia despite increase in insulin resistance. On the other hand diabetes affects TSH responsiveness to TRH and causes low T3.

The present study addressed the possible association of FT3, FT4, TSH with insulin resistance in newly detected hyperthyroid, hypothyroid and euthyroid individuals attending tertiary care hospital in the western part of India.

Material and Methods

We conducted an observational comparative analysis in the SMS Medical College and attached group of Hospitals, Jaipur. The study was carried out with permission of Institutional ethics committee and informed consent was obtained from all the participants.

Sample size

The minimum sample size required was 32 cases in each group at 95% confidence and 80% power to verify the minimum expected difference of (0.47±0.6) in serum insulin level among all 3 groups (euthyroid, hypothyroid and hyperthyroid). This sample size was adequate to study all other study variables too. We took 35 patients in each group.

Subject selection

The subjects were included in three groups.

Group A: 35 newly detected hyperthyroid cases attending the outdoor or indoor wards of SMS Hospital were included.

1Professor and Unit Head, Medicine, SMS Medical College and Hospital, Jaipur, Rajasthan; 2Senior Consultant, Medicine, SN Pareek Memorial Hospital, Kota, Rajasthan; 3Ex-Resident, Medicine, SMS Medical College and Hospital, Jaipur, Rajasthan; 4Assistant Professor, Community Medicine, SK Government Medical College, Sikar, Rajasthan; 5Resident, Medicine, SMS Medical College and Hospital, Jaipur, Rajasthan; 6Assistant Professor, Medicine, Ex-Resident, Pathology, SMS Medical College and Hospital, Jaipur, Rajasthan; 7Corresponding Author

Received: 27.11.2020; Accepted: 28.12.2020
Group B: 35 age and sex matched newly diagnosed hypothyroid cases were included.

Group C: 35 age and sex matched euthyroid individuals were included in this group.

Only individuals more than 18 years of age were included in the study. Patients with known history of diabetes mellitus, polycystic ovarian disease, on drugs affecting insulin resistance, with previous history of thyroid disorder and treatment were excluded from the study. Pregnant and lactating women also were excluded.

Methodology

A thorough history was taken from the finally enrolled study population. Under strict aseptic conditions blood sample was collected by venipuncture for blood glucose, serum insulin, glycated hemoglobin, thyroid hormones, and lipid profile. Other tests done were complete blood count, serum creatinine, blood urea, liver function test. Blood samples were taken after 10 hours overnight fasting.

Thyroid hormones (FT3, FT4), thyroid stimulating hormone (TSH) and serum insulin were estimated using immunoassay systems. The homeostasis model assessment (HOMA) for insulin resistance (HOMA-IR) using the mathematical modeling of insulin concentrations and fasting plasma glucose was estimated. Serum Creatinine was done by modified Jaffe kinetic method, blood glucose, glycated hemoglobin, blood urea by kinetic UV, bilirubin by DMSO colorimetry, transaminases by optimized IFCC method, alkaline phosphatase, GGT, serum total protein by biuret method, serum albumin by BCG method.

Analysis of above parameters was done in SMS Hospital, Jaipur.

Statistical analysis

Quantitative/ categorical data was expressed as percentage/proportion and was analyzed using Chi square test. Quantitative data was expressed as mean and standard deviation and the difference in mean among the three groups was analyzed using one way ANOVA test and post hoc analysis was done for inter group comparison. $P$ value $< 0.05$ was considered as statistically significant. All statistical analysis was done using Epi info version 7.2.1.0.

Results

The mean age of hypothyroid patients was 44.37 years, euthyroid patients was 43.86 years, hyperthyroid patients was 45.24 years. Application of ANOVA test revealed that the three groups were comparable in their mean age ($P > 0.05$). Gender wise distribution showed that in the study, 32 subjects were male and 73 subjects were female.

The difference in mean hemoglobin, total leukocyte count, blood urea, creatinine, total bilirubin, AST level, ALT levels, total proteins, serum albumin, serum globulin levels among study groups were not statistically significant and that the groups were comparable in relation to these parameters.

The mean fasting blood glucose was highest in hyperthyroid group followed by hypothyroid group with the difference in mean fasting blood glucose among study groups being statistically significant ($P < 0.001$) (Table 1). Post hoc Tukey test showed that significant difference was found between hypothyroid and euthyroid group and between hyperthyroid and euthyroid group (Table 2).

The mean HbA1C was highest in hyperthyroid group followed by hypothyroid group with the difference in mean fasting blood glucose among study groups being statistically significant ($P < 0.001$) (Table 1). Post hoc Tukey test showed that significant difference was found between hypothyroid and euthyroid group and between hyperthyroid and euthyroid group (Table 2).

The mean HbA1C was highest in hyperthyroid group and application of ANOVA test showed that difference in mean HbA1C level among study groups was statistically significant ($P < 0.05$) (Table 1). Post hoc Tukey test revealed that significant difference in HbA1C
Table 3: Correlation of HOMA-IR, serum Insulin and FBS with thyroid profile

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>HOMA-IR</th>
<th>Serum Insulin</th>
<th>FBG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>r</td>
<td>P value</td>
<td>r</td>
</tr>
<tr>
<td>Hyperthyroid</td>
<td>FT3</td>
<td>0.706</td>
<td>&lt;0.001</td>
<td>0.649</td>
</tr>
<tr>
<td></td>
<td>FT4</td>
<td>0.314</td>
<td>0.066</td>
<td>0.293</td>
</tr>
<tr>
<td></td>
<td>TSH</td>
<td>0.083</td>
<td>0.637</td>
<td>0.015</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>FT3</td>
<td>-0.204</td>
<td>0.241</td>
<td>-0.219</td>
</tr>
<tr>
<td></td>
<td>FT4</td>
<td>-0.182</td>
<td>0.296</td>
<td>-0.133</td>
</tr>
<tr>
<td></td>
<td>TSH</td>
<td>0.945</td>
<td>&lt;0.001</td>
<td>0.968</td>
</tr>
<tr>
<td>Euthyroid</td>
<td>FT3</td>
<td>-0.361</td>
<td>0.033</td>
<td>-0.338</td>
</tr>
<tr>
<td></td>
<td>FT4</td>
<td>0.040</td>
<td>0.821</td>
<td>0.068</td>
</tr>
<tr>
<td></td>
<td>TSH</td>
<td>0.233</td>
<td>0.177</td>
<td>0.264</td>
</tr>
</tbody>
</table>

was seen only between hyperthyroid and euthyroid patient groups (P<0.05) (Table 2) (Figure 1). The mean insulin was highest in hypothyroid group (15.37 ± 12.63 µIU/ml) followed by hyperthyroid group (10.38 ± 7.56 µIU/ml) and lowest in euthyroid group (4.37 ± 3.11 µIU/ml). Application of ANOVA test showed that the difference in mean insulin level among study groups was statistically significant (P <0.001) (Table 1). Post hoc Tukey test revealed that mean insulin was significantly different in all pairwise group comparisons (Table 2) (Figure 2).

The mean HOMA-IR was highest group in hypothyroid group (3.22 ± 2.69) followed by hyperthyroid group (2.25 ± 1.59) and lowest in euthyroid (0.79± 0.58). Application of ANOVA test showed that the difference in mean HOMA-IR level among study groups was statistically significant (P<0.001) (Table no.1). Post hoc Tukey test revealed that mean HOMA-IR was significantly different between hypothyroid and euthyroid groups and between hyper and euthyroid groups (Table 2) (Figure 3).

In hyperthyroid subjects the calculated Pearson correlation coefficient showed that the serum insulin showed positive correlation with FT3 (r=0.649, P<0.001). HOMA-IR was correlated with FT3 (r = 0.706, P<0.001). Correlation of insulin with FT4 and TSH and HOMA-IR with FT4 and TSH was not statistically significant (Table 3) (Figures 4, 5).

In euthyroid subjects, we observed moderate negative correlation between serum insulin and FT3 (r = -0.338, P=0.047), HOMA-IR and FT3 (r = -0.361, P=0.033). Correlation of insulin with FT4 and TSH and HOMA-IR with FT4 and TSH was not statistically significant.

Discussion

Thyroid hormones have impact on metabolism, energy dissipation and insulin sensitivity. Insulin resistance refers to reduced sensitivity of body tissues like the adipose tissue, muscles even with high or normal levels of insulin in the blood. Increasing body evidence suggests a pattern of multiform combination of biochemical, inherited, and endocrinal defects leading to this pathophysiological interdependence.

Thyroid disease is found to have higher occurrence in females as compared to males. The present study showed that fasting blood glucose was highest in hyperthyroid group followed by hypothyroid group. The intergroup difference was found to be statistically significant. Similar pattern was observed in HbA1C which was highest in hyperthyroid patients followed by hypothyroid patients. HbA1C was lowest in euthyroid individuals. However, the intergroup comparison revealed that only the difference between hyperthyroid and euthyroid mean HbA1C was statistically significant.

The mean insulin levels and HOMA-IR were highest in patients with hyperthyroidism, followed by hyperthyroid patients. These levels were found to be lowest in the euthyroid group. The intergroup analysis showed significant difference between the groups. In the hyperthyroid group, strong positive correlation was seen between serum insulin with TSH, HOMA-IR with TSH. The correlation of insulin levels with FT3, FT4 showed insignificant correlation in this group.

Singh BM et al studied insulin resistance in overt as well as subclinical hypothyroidism. They found increased HOMA-IR in overt hypothyroidism compared to patients with subclinical hypothyroidism and controls. Adhau SR et al found highly significant correlation between HOMA-IR values and TSH in patients with subclinical hypothyroidism. Tuzcu A et al also found higher insulin levels in patients with subclinical hypothyroidism as compared to healthy adults. They also found high levels of hs CRP in these patients suggesting presence of flow grade inflammation.

A possible mechanism suggests reduced blood flow to the peripheral tissues in hypothyroid patients to be accounting for the presence of insulin resistance in these patients. Sapna et al observed higher HOMA-IR in patients with subclinical hypothyroidism than euthyroid individuals and positive correlation for TSH with insulin and HOMA-IR. Similar results were obtained by Maratou E et al who observed insulin resistance not only in clinical hypothyroidism but also subclinical hypothyroidism.

In hypothyroid individuals, impeded insulin mediated glucose utilization by the peripheral tissues has also been a suggested mechanism for insulin resistance. A study investigated insulin directed uptake of glucose by monocytes in patients with hypothyroidism. The authors observed diminished translocation of GLUT4 transporters on the monocytes plasma membranes in this group of patients. This finding was documented in both clinical as well as subclinical hypothyroidism and suggested to be the mechanism resulting in reduced insulin led glucose use by the adipose tissues and muscles.

Hypothyroid patients with diabetes mellitus experience episodes of hypoglycemia. This could be secondary to decreased gluconeogenesis resulting in reduced hepatic glucose output. Hence poor glucose disposal in patients with hypothyroidism may be counterbalanced by a lower delivery in circulation preserving the equilibrium in glucose metabolism.

In the euthyroid group we observed a
moderate negative correlation between serum insulin and FT3, HOMA-IR and FT3, with the correlation being statistically significant. T3 and insulin have similar sites of impact at the cellular and molecular levels in the metabolism of glucose. Hence even minor alterations in the thyroid hormone levels even within the euthyroid range may show insulin resistance. To assess this hypothesis Roos A et al looked into the relationship between metabolic syndrome constituents and thyroid hormone levels in euthyroid individuals. They found significant association of HOMA-IR with TSH and FT4 levels. As FT4 decreased from highest tertile to lowest tertile there was significant rise in HOMA-IR. However in our study, we did not observe significant correlation between insulin resistance parameters and FT4, TSH in the euthyroid subjects group.

On assessing the correlation between the studied parameters in the present study, patients with hyperthyroidism showed strong positive correlation between serum insulin levels and FT3 levels, HOMA-IR and FT3 levels. Hyperthyroidism has been associated with glucose intolerance. Diabetic patients experience deterioration in glycemic control and higher occurrence of episodes of ketosis.

Impact on insulin sensitivity in patients having overt as well as subclinical hyperthyroidism was investigated by Maratou E et al. Both the groups showed higher post prandial glucose levels and higher HOMA index compared with euthyroid groups. They found that at insulin level 100 mU/ml, GLUT 4 levels on monocytes plasma membrane were more in hyperthyroid cases than in patients with normal thyroid function. They also found higher monocytes plasma membrane GLUT3 levels in both, subclinical as well as clinical hyperthyroidism than the euthyroid subjects.

Thyroid hormones have insulin antagonistic influence on the liver. There is reduced glycogen synthesis and higher glycogenolysis. The increased blood glucose in hyperthyroidism is usually due to high endogenous glucose synthesis secondary to higher gluconeogenesis. Animal studies have shown that in rat models the thyroid hormones increase the hepatic expression of glucose transporter GLUT2, leading to increased hepatic glucose output.

Contrary to their effect on the liver, the thyroid hormones exert some actions synergistically with insulin. The glucose disposal by peripheral tissues stimulated by insulin may be increased or normal. The increased substrate requirement for gluconeogenesis in hyperthyroidism may be fulfilled by increased rates of glycolysis and lactate formation compared to glucose oxidation in skeletal muscles. Thyroid hormones have been shown to cause up regulation of GLUT4 or phosphoglycerate kinase.

Induction of lipogenic enzymes by T3 could additionally dysregulate the lipid metabolism characteristic of insulin resistance. Glucose conversion to free fatty acids with simultaneous non inhibited gluconeogenesis sustains the hyperinsulinemic condition.

The bilateral impact between thyroid function and diabetes mellitus has significance in the clinical outcome. It could be hypothesized that correction of thyroid abnormalities in patients suffering from diabetes will enhance glycemic control, diminish cardiovascular risk, and strengthen overall health. However, unanimity regarding guidelines of thyroid status
hypothyroidism. We documented correlation with FT3 in patients with suffering from hypothyroidism. Serum correlation between TSH and we observed significant positive correlation with FT3 in patients with hyperthyroidism. Our study had some limitations also. Being a cross sectional study, we did not study the impact of correction of thyroid hormone abnormalities accompanying insulin resistance in patients with thyroid disorders. It justifies the significance to screen patients with thyroid disorders for evidence of metabolic disorders. This inter relationship between thyroid hormones and insulin could also make way for developing novel targets for future strategies for management of insulin resistance and metabolic syndrome.

**Conclusion**

In this hospital based study we observed significant positive correlation between TSH and HOMA-IR as well as insulin in patients suffering from hypothyroidism. Serum insulin, HOMA-IR showed positive correlation with FT3 in patients with hyperthyroidism. We documented statistically significant higher insulin resistance in patients with hypothyroidism, hyperthyroidism in comparison with the euthyroid individuals.

These findings testify greater hazard of cardiovascular and metabolic abnormalities accompanying insulin resistance in patients with thyroid disorders. It justifies the significance to screen patients with thyroid disorders for evidence of metabolic disorders. This inter relationship between thyroid hormones and insulin could also make way for developing novel targets for future strategies for management of insulin resistance and metabolic syndrome.

**References**

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Ethambutol Optic Neuropathy: Vigilance and Screening, the Keys to Prevent Blindness with the Revised Anti-tuberculous Therapy Regimen

Rohit Saxena, Swati Phuljhele, Anupam Prakash, Rakesh Lodha, Digvijay Singh, Satya Karna, Anant Mohan, Rashmin Gandhi, Vimla Menon, Rajiv Garg and the INOSRG

Abstract
There has been change in the guidelines for the management of tuberculosis in India. The new guidelines advocate the daily use of Ethambutol for both intensive and continuation phase of the treatment. This may be a matter of concern as increased cumulative dose may lead to increase in incidence of toxic optic neuropathy due to ethambutol. Indian Neuro-Ophthalmology Society has taken cognizance of the issue and has come-up with guidelines for prevention and early detection of the toxic optic neuropathy.

Introduction
Ethambutol is an integral drug in the management of tuberculosis. However, an important and well reported side effect of the drug is toxic optic neuropathy which, if not picked up early, can result in variable and often significant visual function loss. The reported incidence of the ocular toxicity varies widely in different studies ranging from 1%-2.5% with the recommended dosages.1-3

In 2019, India notified 24lakh tuberculosis (TB) patients and the estimated TB incidence was 199 patients per 100,000 persons accounting for about 26% of the global incident cases.5 With the aim of elimination of TB by 2025, the Revised National Tuberculosis Control Programme (RNTCP) was revamped in 2016 with changes in the protocol for the management of TB cases.6 The three times a week regimen was changed to a daily regimen and ethambutol was made a part of both the intensive as well as the continuation phase of the treatment.

Although this is expected to enhance compliance and reduce drug resistance, there is an apprehension among ophthalmologists that unless closely monitored, incidence of optic neuropathy can increase multifold and result in significant visual impairment due to increased exposure to ethambutol.

Prevalence
The ocular toxicity of ethambutol is dose and duration dependent.7 The World Health Organisation (WHO) treatment guidelines for Mycobacterium tuberculosis therapy initiation includes an ethambutol starting dose of 15–20 mg/kg per day. At this dose, the toxicity ranges from 1%-3%.1-3 With the increase in dose, the risk of toxicity also increases; with 25 mg/kg/day the risk is 5%-6% and around 18%-30% if the dose is increased up to 30 mg/kg/day.2-9 However, no dose is absolutely safe and toxicity has been reported with doses as low as 12.3 mg/kg.10 Since ethambutol is metabolized by kidney, patients with renal dysfunction are at a higher risk of development of toxicity.

In a large case control study, age greater than 65 years, hypertension, chronic smoking and the presence of renal disease were associated with a greater risk of developing ethambutol toxicity.3 The incidence of toxicity reported by previous Indian studies varies from 0.6%- 3%.11-13 Many patients on ethambutol may not complain of overt vision loss or colour vision deficiency though a substantial number of them may have subclinical toxicity that can be diagnosed on advanced imaging and on electrophysiological tests.14-16

The prevalence of ethambutol optic neuropathy (EON) in children is not well documented but is reported to be lower than that in adults.9 The reason for this is lower serum concentration of ethambutol in children as compared to the adults for a given dose.9 Moreover, the inability to identify any visual impairment in a child makes early identification difficult. In 2010, WHO raised the recommended dose of ethambutol for children to 20 mg/kg per day from the previous 14 mg/kg per day. Even though the prevalence of toxic optic neuropathy is low in children, the risk of the same should always be kept in mind, particularly in preverbal and underweight children.
Pathophysiology

Although the exact mechanism of toxicity remains unknown, one of the principal theories behind ethambutol optic neuropathy has been attributed to its metal chelating property contributing to neurotoxicity. Ethambutol and its metabolite chelate various metal-containing enzymes of the nuclear mitochondria of the cell. This may result in decreased availability of copper in human mitochondria for electron transport chain during oxidative phosphorylation. This results in increase of reactive oxygen species and cascade of events that may lead to cellular apoptosis. Concurrently, it has also been hypothesized that chelation of zinc may activate excitotoxic pathway through lysosomal pathway, which may damage retinal ganglion cells. Retinal ganglion cells, which are the cell body for axons of optic nerve, are particularly susceptible to ethambutol damage due to their high cellular mitochondrial content.

Clinical presentation

Ethambutol toxicity is known to be dose and duration dependent and usually presents between 3-5 months. However toxicity as early as 1.5 months and as late as 12 months of starting the therapy has also been reported.

Patients presenting with EON typically complain of subacute, bilateral, painless loss of vision. Early symptoms include blurred vision, or fading of colour and changes in spectacles. On examination, visual loss is characteristically bilaterally symmetrical, and may range from mild to severe. Colour vision loss is typically seen in green and red spectrum, though blue–yellow colour changes may also occur.

Fundus examination in initial stages is normal, however, in later stages optic atrophy and pallor can be seen temporally more specifically.

Visual field testing most often reveals central or centro-cecal scotoma, though bitemporal visual field defects have also been reported.

Many patients may not have clinical manifestation of the toxicity, however subclinical toxicity can be seen in around 13%-50% of patients as assessed by visual evoked potential (VEP) and optical coherence tomography (OCT).

VEP are the electrical potentials generated at the occipital cortex in response to visual stimulation and are measured as amplitude and latency of the P100 waveform. They reflect electric conduction in the visual pathway. While increased latency in the P100 wave is observed in patients diagnosed with EON, numerous studies have also reported this in asymptomatic patients on ethambutol. However, it is not yet clear how many of these may go on to develop clinical EON.

OCT is a non-invasive imaging of retinal layers where thickness of retinal nerve fibre layer (RNFL) and ganglion cell layer (GCL) can be assessed. OCT changes in form of RNFL thickening and GCL thinning have been reported in symptomatic as well as asymptomatic patients. The role of OCT in management of asymptomatic patients is still not well established.

Treatment and Prognosis

At present, there is no effective treatment for ethambutol induced toxic optic neuropathy. Early detection of the disease and stopping ethambutol may help in preventing further deterioration of visual functions. Ethambutol causes chelation of zinc and copper, thus supplementation of these elements should be considered for the treatment of the disease. Supportive treatment in the form of vitamins, particularly methylcobalamin and pyridoxine (if isoniazid is continued), should be given.

The damage is reversible if discontinuation of ethambutol is done early at the time of onset of toxicity. Around 30%-50% patients show recovery to a variable extent after 6-9 months of stopping ethambutol, with better recovery rate in population younger than 60 years. However, even among patients who show recovery, most patients do not regain normal visual functions and some deficit in visual fields, colour vision or contrast sensitivity remain.

Concerns and Recommendations

According to the new tuberculosis treatment guidelines, the three times weekly regimen has been shifted to the daily regimen of antitubercular treatment (ATT) and ethambutol which was previously part of intensive phase is now included in the continuation phase as well. This change means that ethambutol which was to be prescribed earlier in the 2-month intensive phase only, now needs to be administered throughout the intensive and the continuation phase; meaning a total duration of 6-9 months. Safety has been increased from the previous guidelines by the provision of weight bands for prescription of ethambutol, instead of a fixed dose as in the previous guidelines (Tables 1, 2).

Even with new guidelines, the average dose of ethambutol can reach up to 20 mg/kg/day in adults (Table 1) and 25 mg/kg/day in children (Table 2), particularly for patients on the lower end of the weight band. This risk may be more in conditions like malnutrition, alcohol, tobacco abuse and in associated co-morbidities like diabetes and hypertension. Moreover, concurrent use of isoniazid, which itself is neurotoxic, increases the risk of neurotoxicity. Apart from Ethambutol and INH, Linezolid is also known to be toxic to the optic nerve and simultaneous use of the two medications may increase the chances of optic nerve damage.

The total notified TB cases in India are 21.5 lakhs according to RNTCP report 2019. With the risk of EON of 1% and 3% at dosages 15 mg/kg/day and 20 mg/kg/day respectively, the number of cases suffering from visual impairment could be estimated to range from 22,000 to 66,000, which is not only a significant number but is also preventable.

Measures for Prevention of ethambutol optic neuropathy

As primary prevention is the best way to prevent ethambutol optic neuropathy, it is essential to make health care workers at all levels aware of the side effect of the drug. To increase the awareness among patients and health care providers the information material in form of written instructions or education pamphlets can be provided to physicians, field workers and patients.

Ideally, each patient should undergo baseline ophthalmic evaluation before commencement of the treatment followed by regular evaluation of visual acuity, colour vision and visual fields. However, as it may not be practical to perform these tests in all patients on ethambutol, it is important that patients with high risk factors should undergo baseline ophthalmic evaluation (See Recommendations)
### Table 1: Weight bands for the prescription of ATT

<table>
<thead>
<tr>
<th>Weight category</th>
<th>Intensive phase number of tablets (dose in mg/kg body weight)</th>
<th>Continuation phase number of tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-29 kg</td>
<td>2 (22-14 mg/kg)</td>
<td></td>
</tr>
<tr>
<td>40-54 kg</td>
<td>3 (20.6 – 15.2 mg/kg)</td>
<td>3</td>
</tr>
<tr>
<td>55-69 kg</td>
<td>4 (20 – 16 mg/kg)</td>
<td>4</td>
</tr>
<tr>
<td>≥70 kg</td>
<td>5 (19.6 mg/kg)</td>
<td>5</td>
</tr>
</tbody>
</table>

- HR = Isoniazide, R = Rifampicin, Z = Pyrazinamide, E = Ethambutol fixed dose combination [HRZE - 75/150/400/275 (mg), HRE - 75/150/275 (mg)]

### Table 2: Weight bands for the prescription of ATT in Paediatric age group

<table>
<thead>
<tr>
<th>Weight category</th>
<th>Intensive phase Number of tablets (total ethambutol dose in mg/kg body weight)</th>
<th>Continuation phase Number of tablets (total ethambutol dose in mg/kg body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-7 kg</td>
<td>1 (100 ; 25-14.2)</td>
<td>1</td>
</tr>
<tr>
<td>8-11 kg</td>
<td>2 (20 ; 25-18.2)</td>
<td>2</td>
</tr>
<tr>
<td>12-15 kg</td>
<td>3 (300 ; 25-20)</td>
<td>3</td>
</tr>
<tr>
<td>16-24 kg</td>
<td>4 (400 ; 25-16.7)</td>
<td>4</td>
</tr>
<tr>
<td>25-29 kg</td>
<td>3+1A (575 ; 23-19.8)</td>
<td>3+1A (575 ; 23-19.8)</td>
</tr>
<tr>
<td>30-39 kg</td>
<td>2+2A (750 ; 25-19.2)</td>
<td>2+2A (750 ; 25-19.2)</td>
</tr>
</tbody>
</table>

- A - Adult fixed dose combination [HRZE - 75/150/400/275 (mg), HRE - 75/150/275 (mg)]

and at every 2 month follow-up visits while patients without high risk should undergo screening at 3 and 6 months follow-up visits.

**i. At Physician’s level**

The treating physician may inquire about and record any pre-existing visual impairment. These patients should undergo complete ophthalmic evaluation before starting the treatment and if there is presence of any other optic nerve disorder, ethambutol should be avoided in such scenario. Identification of high-risk patients should be done and their baseline as well as follow-up visits should include ophthalmic screening. On follow-up, patients should be enquired about any visual complaint regarding quality of vision, decreased perception of colour, decrease in visual acuity and central field defect (see Recommendations). The physicians can have a visual acuity chart, and an Amsler’s grid chart at their clinic where screening is possible. Any symptoms/ signs of visual dysfunction should prompt physicians to refer the patient to an ophthalmologist for complete evaluation. In case a significant drop in visual acuity is documented, ethambutol should be discontinued. Treatment in form of vitamins and zinc supplementation should be initiated. If vision loss continues beyond 6 weeks of discontinuation of ethambutol, it may be necessary to stop INH as well.

**ii. At Community Level**

All health care providers, especially the field workers like Accredited Social Health Activist (ASHA) worker or Multipurpose Health Worker (MPWs) should be made aware of the potential side effects of ethambutol and should be included in their training material.

The community health provider who follows up the patient should periodically enquire about visual dysfunction (see box). The health care provider should be trained to urgently refer the patient to the treating physician if patient complains of any visual dysfunction. Vision-related counselling can be provided as a part of Saksham project where a home-based counselling is provided to the patient.

**iii. At Patient’s level**

Patients started on ethambutol and their caregivers should be educated about the possible risk of visual dysfunction. They should be advised to seek care immediately if they notice any visual disturbance. High-risk adult patients could be given an Amsler’s grid or pocket Snellen chart for use at home to test their own vision in between visits to the eye care provider.

**iv. Use of Nikshay App**

Nikshay is a case-based online real-time patient management system which offers the programme managers the ability to monitor their patients real time. This app can be used to identify the high-risk patients and monitor the development of any adverse reaction. The treating physician should note the presence of any pre-existing visual impairment and/or any renal dysfunction in the comorbidities section of the patient’s details. Similarly, if any visual complaint occurs on follow-up, the same should be entered in adverse reaction section of the patient’s follow-up data.

There are various apps available at the google store that have integrated tests for visual acuity, colour vision, and visual fields. These apps can be made available to health care workers at all levels and can be used along with the questionnaire.

It is essential to notify each confirmed case of ethambutol related toxic optic neuropathy with either RNTCP or with the Pharmacovigilance Programme of India (PvPI). This will help in generating the total number of cases with ethambutol toxicity and also identify high-risk characteristics.

### Recommendations

1. Increase awareness among health workers at all levels
2. Identifying the high-risk individuals
   a. patients receiving higher doses (low weight in weight band)
   b. patients receiving for longer duration (Drug resistant TB)
   c. patients with renal function impairment
   d. co-existing Diabetes Mellitus
   e. tobacco/alcohol abuse
   f. combined therapy with Linezolid
   g. pre-existing visual dysfunction
   h. young (preverbal) children
3. All high-risk patients to undergo baseline examination which includes visual acuity, colour vision and visual fields and at every 2 months follow-up visit.
4. Non-high-risk patients should undergo examination at 3 and 6 months follow-up visits.
5. At Physician’s Level
   a. Ask for history/ complaint of any ophthalmic disorder before starting treatment
b. Ethambutol should be avoided in presence of pre-existing optic neuropathy

c. Make patients aware of the side-effects of ethambutol, without raising alarm

d. On follow-up, patient should be asked for any visual dysfunction

i. Fading of colours

ii. Decrease in visual acuity/blurred vision

iii. Presence of any scotoma (non-seeing area) in the central field

e. The examination can be done by physicians using a visual acuity chart, a red coloured object and an Amsler’s field chart kept in his/her clinic

f. On development of any visual complaint, patient should be referred to an eye specialist and ethambutol should be stopped until a complete ophthalmic evaluation is done

g. If the diagnosis of ethambutol toxicity is confirmed, ethambutol should be replaced for remaining duration of the treatment

h. INH should be discontinued if the vision loss continues beyond 6 weeks of discontinuation of ethambutol

6. At Community level

a. Creating awareness among community health care providers like ASHA workers

b. At follow-up visits at home or at centre, a questionnaire with following questions can be administered.

i. Is there any loss of vision or blurred vision

ii. Do colours appear faded?

c. The field worker must refer the patient to the treating physician if patient complains of any visual dysfunction.

7. At Patient’s level

a. They must be educated about the possibility of visual dysfunction.

b. They must be made aware about the need to seek care immediately if they notice any visual disturbance

c. Patients could be given an Amsler’s grid or pocket Snellen chart for use at home to test their own vision in between visits to the eye care provider.

8. Use of Nikshay App

a. Recording of any pre-existing visual impairment and renal function impairment in the patient’s details

b. Any visual disturbance should be recorded under adverse reaction section in the patients follow up data

9. Consider use of App-based tests for visual screening at community level or at physician’s level

10. Notification of a confirmed case of Ethambutol toxicity either with RNTCP or with Pharmacovigilance Programme of India

Acknowledgement

We wish to acknowledge the support of Cipla Ltd. in the conduct of the virtual meeting and the support in the drafting of the document.

References


New and Unique Clusters of Type 2 Diabetes Identified in Indians

Ranjit Mohan Anjana¹, Rajendra Pradeepa¹, Ranjit Unnikrishnan¹, Mangesh Tiwaskar², Sosale R Aravind³, Banshi Saboo⁴, Shashank R Joshi⁵, Viswanathan Mohan⁴

Abstract

Type 2 diabetes (T2D), the most common form of diabetes, is recognized as being a heterogeneous disorder, and presents a universal threat to health. In T2D, the pathophysiology and phenotype differ significantly by ethnicity, particularly among Asian Indians, who are known to have the ‘Asian Indian phenotype’, which makes them more susceptible to develop T2D than white Caucasians. The recent subclassification of T2D into different subtypes or clusters, which behave differently with respect to clinical presentation and risk of developing complications is a remarkable development. Five unique “clusters” of individuals with diabetes were described in the Scandinavian population [Severe Autoimmune Diabetes (SAID), Severe Insulin Deficient Diabetes (SIDD), Severe Insulin Resistant Diabetes (SIRD), Mild Obesity-related Diabetes (MOD) and Mild Age-Related Diabetes (MARD)]. For the first time in India, identification of clusters of diabetes was done on 19,084 individuals with T2D, using 8 clinically relevant variables (age at diagnosis, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol and fasting and stimulated C-peptide). Four replicable clusters were identified [SIDD, MARD, IROD (Insulin Resistant Obese Diabetes) and CIROD (Combined Insulin Resistant and Deficient Diabetes)], two of which were unique to the Indian population (IROD and CIROD). Clustering of T2D helps i) to accurately subclassify diabetes into different subtypes, ii) plan therapies based on the pathophysiology, iii) predict prognosis and prevent diabetic complications and iv) helps in our approach to precision diabetes. Further studies would help us to refine the usefulness of these clusters of T2D particularly in the Indian population, with respect to selection of appropriate therapies and hopefully in the prevention of complications of diabetes.

Introduction

Diabetes is a heterogeneous group of disorders characterized by chronic hyperglycemia due to disturbances in carbohydrate, protein and fat metabolism, which result from either a defect in insulin action or secretion or a combination of the two.¹ Type 2 diabetes (T2D), the common form of diabetes, spans a spectrum of pathophysiology, from those with severe insulin resistance with near-normal beta-cell function at one end to those with normal insulin sensitivity with severe beta-cell secretory defect at the other.² The current management approaches have not been able to prevent the progression of diabetes and associated chronic complications. One of the reasons could be that T2D is diagnosed and treated as if it is one homogenous condition, although the disease is highly heterogeneous with respect to its clinical presentation, progression, treatment patterns and susceptibility to complications.³ Over the past couple of years, attempts have been made to identify subgroups or “clusters” of individuals with T2D using metabolic traits, which behave differently with regard to phenotype, clinical presentation and risk of complications.⁴,⁵ In addition, efforts to address diabetes heterogeneity have also been investigated using genetic markers.⁶,⁷

Evolution of Classifications of Diabetes

An important step in understanding the etiology of diabetes requires identification of its various forms and subtypes. While several sets of criteria have been proposed for diabetes, no systematic classification existed until the 1960s. A few decades ago, diabetes was classified as “maturity” or “growth onset” diabetes based on the age at diagnosis of the disorder. In 1980, the World Health Organization (WHO) Expert Committee classified diabetes mellitus as “insulin dependent” (later called type 1 diabetes) and “non-insulin dependent” diabetes (later called type 2 diabetes) depending on the need for insulin for survival or maintaining good health. Their classification system also included “other types of diabetes” and gestational diabetes mellitus (GDM).¹² The American Diabetes Association (ADA) classified the disorder into four major types based on presumed etiology.¹³ The four major types include type 1 diabetes (presence of autoantibodies against pancreatic islet β-cell antigens and younger age at diagnosis); type 2 diabetes (absence of autoantibodies and characterized by insulin resistance with relative insulin deficiency and older age at diagnosis); GDM (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation); and specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (eg. glucocorticoid...
use, in the treatment of HIV/AIDS, or after organ transplantation.\textsuperscript{15}

**Is Type 2 Diabetes One Disease or Several Subtypes?**

T2D is the most common type of diabetes present worldwide.\textsuperscript{14} About 10\% patients diagnosed to have T2D could actually have latent autoimmune diabetes of adults (LADA),\textsuperscript{15} while another 1-\% may have autosomal dominant inherited forms of maturity-onset diabetes of young (MODY),\textsuperscript{16} and 1\%, rare genetic mutations. The majority (85\% - 90\%) however, have the common \textquoteleft garden variety\textquoteright of T2D. T2D is caused by a combination of genetic and environmental factors.\textsuperscript{17} The clinical features of this widely prevalent form of T2D shows marked heterogeneity. Hence, subclassification of individuals with T2D into distinct clusters could help in assessing prognosis and deciding management of individuals at high risk for developing complications.

**Earlier Studies on Subtypes of Type 2 Diabetes**

Maldonado et al\textsuperscript{18} in 2003, reported on the classification of four groups of diabetic patients (n=103), of various ethnic groups, who presented with diabetic ketoacidosis (DKA) based on the presence or absence of islet autoantibodies (A+/−) and evidence of beta-cell functional reserve (B+−/−). Based on these criteria, four groups: A B−(50\%), A B+ (22\%), A B+ (17\%), and A B+ (11\%) were identified. Another study undertaken by Li et al\textsuperscript{19} in 2015, used electronic medical record data of T2D individuals (n= 2551) and 73 clinical features for topology-based patient-patient network generation. Three distinct subgroups of T2D were identified by this group which included i) Subtype 1 (29.8\%), characterized by diabetic nephropathy and retinopathy; ii) Subtype 2 (24.2\%), associated with cancer and cardiovascular diseases; and iii) Subtype 3 (43.0\%), strongly associated with cardiovascular and neurological diseases, allergies and HIV infections. In addition, they also reported unique genetic associations to the subtypes, which included 1279, 1227, and 1338 SNPs that mapped to 425, 322, and 437 genes specific to subtypes 1, 2, and 3, respectively. This study provided an example of the potential use of large-scale data and machine-learning approaches to subtype complex disease; however, replication of these subgroups was not done to confirm these findings.

**Identification of New Clusters Among Type 2 Diabetes**

The field of clustering of T2D really took off after a novel diabetes subclassification was identified in a Scandinavian population by Ahlqvist et al.\textsuperscript{4} They reported five unique \textquoteleft clusters\textquoteright of individuals with newly diagnosed diabetes (n=8980) using a data-driven approach, and six clinical variables measured at the time of diagnosis, which included glutamic acid decarboxylase (GAD) antibodies, age at diagnosis of diabetes, body-mass index (BMI), glycated hemoglobin (HbA1c), homeostasis model assessment of insulin resistance (HOMA 2-IR) and beta-cell dysfunction (HOMA2-β). These five diabetes subgroups were termed as SAID (Severe Autoimmune Diabetes), SIDD (Severe Insulin Deficient Diabetes), SIRD (Severe Insulin Resistant Diabetes), MOD (Mild Obesity-related Diabetes) and MARD (Mild Age Related Diabetes).\textsuperscript{4} The five clusters varied in clinical characteristics, progression and outcomes of diabetes. Following the identification of new diabetes clusters in the Scandinavian population, these clusters were tested for replicability in various other populations to see if this classification is applicable to individuals with diabetes in other ethnic groups. While the Scandinavian clusters were replicated in some populations, in others they could not be fully replicated.\textsuperscript{5,9}

**Novel Clusters Identified in Indians**

**Why look for clusters in Indians?**

T2D in Asian Indians differs from Caucasians in a number of significant ways. Asian Indians have several unique characteristics which are collectively called as the \textquoteleft Asian Indian phenotype\textquoteright such as younger age at diagnosis, less severe obesity, increased insulin resistance etc.,\textsuperscript{19,20} which may account for their increased predisposition to develop T2D.

**Figure 1** presents the characteristics of the \textquoteleft Asian Indian phenotype\textquoteright.\textsuperscript{21-30} It is therefore possible (due to the above and the well-known younger age at diagnosis) that clusters of type 2 diabetes identified in Asian Indians based on parameters used in the Western population might not behave exactly in the same manner with respect to treatment outcomes and risk of complications. Hence, we wanted to look for clusters of T2D in Indians.

**Indian Discovery Cohort**

Using data from a tertiary diabetes centre in Southern India, clustering of diabetes was conducted in individuals with T2D (n=19,084), using 8 clinically significant variables (age at diagnosis, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol and fasting and stimulated C-peptide).\textsuperscript{9} Four clusters of patients were identified in the Indian population, which varied in characteristics as well as disease outcomes with regard to the management of diabetes and risk of complications. Of the four clusters identified in Indians\textsuperscript{7} two were similar to that identified in the Scandinavian population, while two were unique.

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\textsuperscript{1} **Fig. 1:** ‘Asian Indian Phenotype’\textsuperscript{21-30}
The phenotypic characteristics of the study population respectively. were present in 25.9% and 12.1% of Insulin Resistant Obese Diabetes (IROD) and Insulin Resistant Obese and Deficient Diabetes (CIRDD), respectively. The two newly identified groups in the Scandinavians, were SIDD (Severe Insulin Deficient Diabetes) and IROD. The two clusters similar to Indians. The two clusters similar to those in the Scandinavians, were SIDD and IROD which were present in 26.2% and 35.8% of the patients respectively. The two newly identified groups IROD (Insulin Resistant Obese Diabetes) and CIRDD (Combined Insulin Resistant and Deficient Diabetes) were present in 25.9% and 12.1% of the study population respectively. The phenotypic characteristics of the four clusters identified among Indians differed significantly from each other as shown in Figure 2. The characteristics of the clusters did not differ when split by gender and duration of diabetes (< 1 and < 3 years), which shows the stability of the clusters.

Indian Replication Cohort

The clusters identified in the Indian cohort were also replicated in the nationwide representative population-based ICMR-INDBIA study conducted across 15 Indian states/Union territories, showing that the four clusters identified are truly representative of the Indian population. In the INDBIA population, 34.8% of the population were in the MARD cluster, 30.3% in the IROD cluster, 24.7% in SIDD and 7.6% in the CIRDD cluster. Lowest BMI and waist circumference were observed in the SIDD group, who had the poorest glycemic control. IROD had the highest waist circumference and BMI, while the CIRDD cluster had the highest triglycerides, diastolic blood pressure, HbA1c, and lowest HDL. Highest age at diagnosis of diabetes, HDL levels and low diastolic blood pressure levels were observed in the MARD group. This group also had the mildest diabetes and therefore the best metabolic control.

This study also investigated the risk for microvascular complications of diabetes among the different subgroups (Figure 3) and reported that SIDD had the highest prevalence (4.9%) and risk for developing diabetic retinopathy [Hazard ratio (HR):1.6]. Conversely, CIRDD had the highest hazards for diabetic nephropathy (HR:1.2) while IROD (HR:1.5) and CIRDD (HR:2.3) had greater risk for chronic kidney disease after adjusting for confounding variables namely age, gender, blood pressure and HbA1c compared to MARD. The novel cluster CIRDD is of particular importance as it is characterized by difficult-to-control hyperglycemia and increased risk of both diabetic eye and kidney disease.

What is the Clinical Relevance of Identifying Clusters of Type 2 Diabetes?

Sub classification of individuals with T2D into distinct clusters has important implications for prognostication and management of patients. Individuals with the “mild” subtypes of T2D may require less aggressive management of hyperglycemia, particularly if they are in the elderly age group. On the other hand, individuals with a combination of severe insulin resistance and profound insulin deficiency appear to be the worst off when it comes to glycemic control as well as risk of complications. These patients will benefit from early aggressive treatment of hyperglycemia, using drugs that target a multitude of pathophysiologic mechanisms.
Identification of clusters also has an important bearing on the selection of the most appropriate anti-diabetic therapy. For instance, individuals with insulin-deficient diabetes (SIDD) which would benefit the most from early initiation of insulin-providing therapies while those in the IROD cluster would perhaps benefit more from therapies which tackle insulin resistance. Gan et al. have shown that individuals of Asian Indian ethnicity respond differently to various classes of anti-diabetic medication compared to white Caucasians. This systematic review and meta-analysis concluded that the glucose-lowering efficacy of SGLT-2 and DPP-4 inhibitors, was greater in Asian Indians compared to white Caucasians.

Conclusion

In summary, the classification of T2D in Indians into phenotypic subtypes offers insights into the pathophysiological processes that drive diabetes in this ethnic group. This could aid in predicting the risk of diabetes complications. Identification of distinct subgroups of individuals with T2D could also have important implications for optimal management as well as prognostication, and this is an important initiative towards “Precision Diabetes”. Table 1 summarizes the benefits of clustering of T2D. Further studies along these lines would help us to refine the various clusters of T2D in the Asian Indian population, particularly with respect to selection of appropriate therapies and thus in the prevention of complications of diabetes.

Table 1: Advantages of clustering of diabetes

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helps to accurately subclassify diabetes into different subtypes</td>
<td>Helps to plan therapies based on the pathophysiology</td>
</tr>
</tbody>
</table>

Targets, as well as early and regular screening for development of chronic vascular complications.

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Effective Written Communication in Consult Letters: A Crucial Yet Overlooked Skill?

Raman Deep

Abstract
The consult letters can be viewed as a window to the entire consultation process. Suitable drafting of consult letters is a useful but often overlooked skill in training years. It is not uncommon to find the consult notes lacking the relevant context or clinical information. Both the style and content should be kept in mind for an effective written communication. It is also important to supervise and give specific feedback to the trainees to make the consult letters succinct and clear.

Table 1: Common concerns related to consult letters

<table>
<thead>
<tr>
<th>Common concerns of referring clinicians</th>
<th>Common concerns of referring clinicians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of a clear reason for the referral</td>
<td>Delay in attending a consultation</td>
</tr>
<tr>
<td>Noted reason does not seem satisfactory (e.g. too broad or non-specific)</td>
<td>No specific feedback provided</td>
</tr>
<tr>
<td>No mention of key clinical findings</td>
<td>Excessive, over inclusive details, while a clear recommendation is missing</td>
</tr>
<tr>
<td>Test results and details of previous treatments not provided</td>
<td></td>
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</table>

Benefits of efficient communication in consultation

There are several direct and indirect benefits in inculcating the practice of effective consult letters, as below:-

a. Forms a documentation or record of the patient assessment for posterity
b. Forms a treatment recommendation for patient
c. Helps to remember the patient details and plan during periodic follow-ups
d. Enhance the working relationship with the referring physician
e. Helps in the medicolegal requirements
f. Occasionally, serves to disseminate the informative or educative material

Poor communication can lead to several problems by means of unnecessary tests, repetition of investigations, unnecessary exposure to overlapping medications with similar mechanism of action, delayed diagnosis and poorer outcomes.

Overcoming the barriers in efficient communication

Several problems and issues may be faced by both the consulting and referring clinician during the process of consultation. There may be dissatisfaction among both parties regarding the consultation. Some common concerns are summarized in Table 1.

It is not uncommon to find the requests/referral letters which lack sufficient details on relevant context or clinical information leading on to consultation, as below:

Case I: “Mrs X is seen to be angry since yesterday evening. Please see the patient”
Case II: “Mr Y is known case of diabetes. He is not eating well. Kindly see him”
Case III: “Mr Z seems to have fever. Kindly come and check.”

Instead of insisting on immediate revisions, in such scenarios, it is better to personally talk to the consultee and explore about the precise reason for consultation, requesting them to mention the same in future referrals. Further, it is often useful to inculcate and nurture a working relationship across various specialties, rather than create barriers to consultation.

Occasionally patients may be surprised to learn that a consultation has been requested by their treating team. If not prepared adequately, they may also be uncooperative towards assessments, for example a psychiatric consultation requested by a physician may be met with some resistance by patients who may not feel the need. Therefore, it is a good practice for the treating physician to disclose the reasons, scope and possible benefits of consultation beforehand.

Approach

Briefly, the consult letter is the written record of the step-wise approach to a consultation. This should include the following steps:

1. Receive a formal consultation request: It is useful to insist on a formal written consultation request/referral letter in all routine cases. This is useful for documentation purposes and to understand the case highlights.

2. Speak to the consulting clinician (to clarify and understand reasons

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Received: 12.02.2020; Accepted: 16.07.2020
for referral): Whenever required, it is a good idea to personally talk to the referring clinician to clarify. Talking personally always yields additional useful information about patient. Further, if patient has not been informed yet, it may be a good idea to ask the referring clinician to let the patient know to expect a consultation.

3. Determine the scope of consultation: The issues of immediate clinical concern should be resolved first, and long term issues may be attended later on out-patient basis.

4. Review the chart yourself: Always personally review the chart of the patient for cross-checking the current medications and their dosages, and to look for any adverse effects or drug-drug interactions.

5. Interview the patient, family and collateral informants

   Introduce yourself to the patient and family members. If there are any visitors, they can be asked to wait outside. Emphasis must be given to gather information from more than one caregiver, if needed. For example:- the family member who stays at night-time may be different from day caregiver, and may be a better informant for ‘delirium’ or ‘sun-downing’ phenomenon. Similarly, the nursing staff, ward attendants (and if patient permits, even the neighbouring patients or their attendants) can provide the first-hand account especially in the context of any behavioral changes observed by them. These sources provide valuable additional information.

6. Write the consult letter

   The content and style of the consult letter is discussed later.

7. Speak to the consulting clinician (for patient feedback and discuss any key issues)

   Talking to the consulting clinician, either in person or over telephone, is especially important to communicate the brief plan and discuss any issues in clinical management. It also helps to develop and nurture the relationship and trust between specialties.

8. Follow up arrangements: These must be clearly mentioned in consult letter including days and timings for out-patient follow ups post-discharge.

Drafting a Consult Letter

Both the style and content of the consult letter need to be kept in mind for an effective written communication, in addition to certain practical tips and strategies.1,2,3

I. Style:

   The visual layout of the letter is very important in making it easier to grasp the important information by the reader. Overall, the consult letter must be written clearly and briefly. Attention must be paid to ensure the following:

   It is as succinct as possible
   Trade the long, complex sentences with simple and lucid ones
   One idea per sentence (as a rule)
   Organized as brief paragraphs (~4-5 lines)
   Using only 2-3 headings in a page
   Use bullet points for items such as medications or management plan
   Always begin or end by thanking the clinician for referral
   Always maintain a professional tone and attitude (avoid ‘note wars’)
   Avoid the excessive use of passive tone in consult letter
   Try to understand the perspective of the referring clinician

II. Content

For consultation letters, identify:
- essential content (crucial)
- helpful content (desirable)
- excessive content (avoidable)

In order to be thorough, the content should proceed according to a pre-determined structured format, especially during the residency years, with a scope for flexibility.3,8

The specific content of consult letter may vary from one specialty to another, and would also depend on the kind of medical queries, if any, posed by the treating team.

Broadly, the content of the reply to consult letter covers the following aspects:

   - Begin with date of assessment (and preferably, time of the day)
   - Patient’s socio-demographic data, bed and ward number, hospital registration number
   - Identifying information (birthmark etc in medico-legal assessments)
   - Informants and sources of information
   - Brief history and evaluation findings
   - Provisional diagnosis and/or differential diagnosis, with supportive evidence
   - Management plan
   - Need for further investigations, as relevant, e.g. urinalysis for drug use, serum drug levels, special blood tests or neuroimaging etc
   - List of medications to be avoided, if relevant
   - Any psychoeducation or other intervention provided to patient
   - Need for periodic monitoring must be documented.
   - A clear and brief answer to the referring physician’s specific question/s, if any

Signature

Need to maintain records?

It is understandable that the consulting clinician may have gathered substantial information which is not too relevant to write in consult letter itself. Further, some information shared by patient may have been confidential and cannot be explicitly mentioned in consult letters for ethical or legal reasons. Therefore, it is often advisable to maintain a separate file or record of consultations containing detailed information while more concise notes can be put in consult letters. This system of maintaining separate records can serve the purpose of documentation for future record and facilitate the follow-up visits, especially for chronic relapsing disorders.

III. Practical strategies
Treatment decisions must be collaborative. In situations where patient is being managed by two or more specialties, the treatment is a collaborative effort, and decisions cannot be taken unilaterally. For example, if psychiatrist finds the use of steroids to exacerbate psychosis, then it is important to discuss with treating team to understand the immediate risks vs benefits of steroids for underlying medical condition. The risks have to be balanced against benefits, and accordingly the plan may vary from discontinuation to dose reduction to adding psychotropic medications, in case steroids cannot be stopped.

The clinical condition may be fluctuating e.g. delirium, requiring periodic monitoring. Even if patient is asymptomatic at the time of assessment, one must give due credence to recent history, rather than dismissing it. In such cases, it may be pertinent to make another visit and/or may educate the treating physician to monitor and record.

The consultant should avoid speculations for future in the consult letters even if specifically asked to do so. Lines such as ‘this patient will have capacity for consent after psychosis is resolved’ must be avoided at all costs. Instead, assessment should be planned for a later date for a fresh assessment.

Provision of too much information or too little information is problematic. Providing too much information is often boring and confusing for the physicians, who are unlikely to read it (which defeats the purpose of consultation). As discussed earlier, such extra information may be noted in a separate case file kept. Providing too little information does not serve to communicate the management aspects or clarify the reasons for recommendations.

Always use a non-judgemental tone in the consult letters.

Deferring the overall leadership of patient management to the consulting physician: It is important to understand that the patient is admitted under the care of referring physician. One can give advice on issues which concern the area of expertise of the consulting clinician, however one cannot enforce his/her perspective, on other treatment decisions such as length of hospitalization or nature or doses of drugs for co-occurring medical disorders. Any disagreements or concerns must be resolved by mutual discussions, and any specific professional advice must be documented in a neutral tone in the consult letters.

Teaching methods and tools

Suitable drafting of consult letters is a useful skill learned early on in the residency training. Further, it can be incorporated as a routine only if adequate practice and feedback is given in training years. Equally important is to make the trainees understand the reader’s perspective on how information will be used or understood by the readers at the other end.6

It is important to supervise and give specific feedback to the trainees to make the letters succinct and clear

It is useful to develop structured templates for use in training. A template can be a useful tool for organizing content and assist in writing effectively in early years of training. (structured templates)

The use of case vignettes may help in honing skills towards precisely drafting the consult letters. The case vignette method may be useful for teaching or training purposes as well as for assessment of the progress.

The role plays conducted in small groups can serve as methods for demonstrating role of efficient communication skills.

Scope for research

There is an inadequate amount of evidence based research on optimum content or preferences pertaining to consult letters, or their impact on patient outcomes. In a recent review of Embase, Medline and Cochrane databases, Rash and colleagues sought to determine the components of a consult letter which are of most value to the referring physician. Eighteen articles were included in synthesis, which found that the referring physicians prefer brief, structured letters that feature diagnostic, prognostic and management plans over unstructured letters featuring detailed histories and other findings. The report favored the synthesis, insight, and formulation of consultant who attended the patient, over the voluminous data that underpins that synthesis.10 Such research can inform the practice.

Conclusion

To conclude, the consult letter is the window to the entire approach and process of consultation. The goal of written communication is to remove rather than create barriers to patient care across specialties. Special attention must be paid to the content and style of the consult letter. The structured format, with scope for flexibility, may serve well during the residency years, along with periodic feedback on quality of consult letters.

Disclosure

*The content was presented by the author in form of lecture in workshop “Communication with the non-physiatrist: evolving a common language’ at National CME for Consultation psychiatry held at A.I.I.M.S., New Delhi, April 9, 2018.

References

Seven-and-a-Half Syndrome

Meenaxi Sharda¹, Prateek Jain², Nitesh Kumar Bauddh³, Jitendra Kumar Meena², Yashwant Sharma²

A 78 year old hypertensive and controlled diabetic (RBS-104mg/dl, HbA1c 6.2%) female presented with sudden onset deviation of angle of mouth to left side, slurring of speech and inability to close right eye from 2 days. There was no history of headache, vomiting, fever, head trauma, seizure and weakness in any limb. General physical examination was within normal limits except blood pressure (190/100mm Hg). There was right lower motor neuron facial palsy (Figure 1) along with impaired right eye adduction and nystagmus in abducting left eye on left lateral gaze suggesting right internuclear ophthalmoplegia (Figure 2). No other neurological abnormality. MRI brain showed subacute infarct in right pons (Figure 3) and multiple chronic lacunar infarcts. Figure 4 shows the recovering picture of the patient after a month.

Discussion

Internuclear ophthalmoplegia (INO) is a well known clinical entity characterized by impaired ipsilateral eye adduction with nystagmus in contralateral abducting eye on attempted lateral gaze with preserved convergence. It results from damage to the ipsilateral medial longitudinal fasciculus (MLF) ascending from abducens nucleus in the pons to the oculomotor nucleus in the midbrain. One-and-a-half syndrome is characterized by horizontal gaze palsy with ipsilateral INO due to lesion of the MLF combined with a lesion of the paramedian pontine reticular formation (PPRF) on the same side. If the adjacent ipsilateral facial nucleus, situated in pons, also gets involved leading to lower motor neuron facial paralysis, it becomes eight-and-a-half-syndrome (seventh cranial nerve+ one and a half syndrome). This lady had right internuclear ophthalmoplegia along with right lower motor neuron facial palsy and no ipsilateral horizontal gaze palsy suggesting a lesion involving only right MLF and right facial nucleus, which is denoted as seven-and-a-half syndrome. To the best of our knowledge this is a new entity. Literature search revealed that the term “Seven and a half syndrome” was introduced and coined by Ama Sadaka et al¹ in the article published in scientific literature in 2017.

References


Fig. 1: Right lower motor neuron facial palsy
Fig. 2: Right internuclear ophthalmoplegia. Failure to adduct right eye with left abduction nystagmus on left lateral gaze. Right gaze is normal
Fig. 3: MRI brain T2W and FLAIR showing subacute infarct right pons
Fig. 4: Recovery in right lower motor neuron facial palsy and right internuclear ophthalmoplegia after 1 month
Quadricuspid Aortic Valve

Prajit Mazumdar¹, Prabin Shrivastava², Vidyapati³, Malyaban Das⁴

Quadricuspid aortic valve (QAV) is a rare variant of abnormal development of semilunar valves.

It is far less frequent (incidence of 0.043% by two-dimensional transthoracic echocardiography)¹ as compared to bicuspid (1–2%) or unicuspid aortic valve anomaly.

The functional status of QAV is predominantly a pure AR.

The functional status of QAV is regurgitant in 74.7%, combined stenosis and regurgitation in 8.4%, stenotic in 0.7%, and normally function is seen in 16.2%.²

Quadricuspid aortic valve is associated with other congenital anomalies in tune of 18.3%.²

These congenital anomalies include coronary artery abnormalities, ventricular septal defect, patent ductus arteriosus, pulmonary stenosis, ruptured sinus of Valsalva, complete heart block, and hypertrophic cardiomyopathy.

Moreover in QAV with unequal cusps, uneven distribution of stress and incomplete juxtaposition during diastole may lead progressive aortic insufficiency and gradual deterioration over the years, and thus increasing the risk of complications like endocarditis and left ventricular failure (LVF).

Hence, in all patients with aortic regurgitation or aortic regurgitation with stenosis, QAV should be searched for and once diagnosed, QAV patients should be frequently followed up so that aortic valve replacement or repair is done before the onset of complications like infective endocarditis or LVF to reduce morbidity and mortality.

References

SPEEDY RELIEF GETS A NEW LOOK

Abbreviated Prescribing Information

**Liquid Paraffin, Milk of Magnesia and Sodium Picosulphate Oral Emulsion**

**CREMAFFIN PLUS**

**COMPOSITION:** Each 5 ml (1 teaspoonful approx.) contains: Liquid Paraffin 1.8 ml, Milk of Magnesia 1.75 ml, Sodium Picosulphate 0.6 mg. Colour: Carmoisine & Ponceau 4R. **INDICATION:** For the symptomatic relief of constipation in adults. **DOSE AND ADMINISTRATION:** Adults and children over 12 years: 7.5 ml (approx. 1.5 teaspoonfuls) if the response is unsatisfactory, the dose may be increased to 15 ml (3 teaspoonfuls) or as advised by the physician. Children 3 to 12 years: 1 teaspoonful or as advised by the physician. Children 3 to 5 years: As advised by the physician. **CONTRAINDICATIONS:** Patients with hypersensitivity to liquid paraffin, magnesium hydroxide or sodium picosulphate. Presence of intestinal obstruction, ileus, toxic megacolon, gastric retention, abdominal pain, nausea or vomiting, and in children under 3 years of age. **WARNINGS AND PRECAUTIONS:** In patients with renal impairment, cardiac arrhythmias, colonic mucosal ulceration, ischemic colitis and ulcerative colitis. Use in Patients with Significant Gastrointestinal Disease. Prolonged use is not recommended. **PREGNANCY AND LACTATION:** The safety of Cremaffin Plus for use in pregnancy and lactation is not established. Therefore, as with other medicines, Cremaffin Plus should not be administered during pregnancy and lactation. **ADVERSE REACTIONS:** Liquid paraffin may cause mouth dryness and irritation, granulomatous reactions. Nausea, headache, and vomiting are the most common adverse reactions. **OVERDOSE:** Gastric lavage may be performed where appropriate. Treatment should be symptomatic and supportive. **Issued on:** 5th Nov 2018. **Source:** Prepared based on full prescribing information version v3.0, dated: 29th Oct 2018. **Trademark of the Abbott Group of Companies.**
Primary Central Nervous System Lymphoma (PCNSL) - A Rare and Unusual Presentation of Rapidly Progressive Major Cognitive Dysfunction

Laxmi Nand¹, Dalip Gupta², Sunil Sharma³, Suresh Kumar⁴

Abstract
Primary central nervous system lymphoma (PCNSL) is a rare, extranodal non-Hodgkin’s lymphoma arising within and confined to central nervous system (CNS) involving the brain, leptomeninges, spinal cord or eyes. Bailey in 1929, reported the PCNSL for the first, termed ‘perithelial sarcoma’. PCNSL accounts for less than 5% of all primary CNS malignancies and for 1 to 2% of all lymphomas. Few recent studies especially from UK and USA have reported an increase in the incidence of PCNSL both in immunocompromised and immunocompetent subjects. However, the studies from India and few from abroad did not report any increase in the incidence of PCNSL despite increase in the incidence of acquired immunodeficiency syndrome (AIDS). Studies did not report PCNSL as a frequent cause of major cognitive dysfunction or dementia. Primary brain tumor itself exists as a less frequent cause of dementia. We describe a case of PCNSL as a rare and unusual presentation of rapidly progressive major cognitive dysfunction which revealed clinicopathologically evident marked improvement after treatment, ascribing PCNSL as potentially reversible cause of major cognitive dysfunction.

Introduction
Primary central nervous system lymphoma (PCNSL) is a rare form of extranodal non-Hodgkin’s lymphoma confined to craniospinal axis. PCNSL accounts for less than 5% of all primary CNS malignancies and 1 to 2% of all lymphomas. Amongst the causes of major cognitive dysfunction, primary brain tumor exists as a less frequent cause. We report a case of PCNSL as a rare and unusual presentation of rapidly progressive cognitive dysfunction which revealed clinicopathoradiological correlation. The patient revealed clinicoradiologically evident marked improvement after treatment, ascribing PCNSL as potentially reversible cause of major cognitive dysfunction.

Case Report
76 years old male, ex-smoker, non alcoholic, non hypertensive and non diabetic was hospitalised with headache of three months duration, severely increased holocranially since one week, rapidly progressive forgetfulness, difficulty in navigation and performing activities of daily living and visual hallucinations, for the last three weeks. Examination revealed blood pressure of 130/78 mm of Hg, pulse rate of 72 beats per minute, no lymphadenopathy or organomegaly, and normal respiratory and cardiovascular system. Neurological examination revealed normal fundoscopy, mini mental status examination (MMSE) score of 9/30 with markedly reduced orientation to time, place and space, loss of recent and remote memory, apraxia and bradykinesia without any other deficit. Investigations revealed normal blood count with Hb of 16 gm%, biochemistry, thyroid functions, lipid profile, urine analysis, ECG, chest radiogram, and ultrasonogram of abdomen. CSF analysis revealed proteins of 160 gm%, sugar of 67 gm%, no WBC or malignant cells and TB-PCR detection. HIV serology and VDRL were negative. In radiomages, CT thorax and abdomen revealed no lymphadenopathy and organomegaly, non-enhanced CT (NECT) head revealed hypodense lesions bilaterally in thalamic regions with perilesional edema and a soft tissue density lesion at right skull base (Figure 1a and b), conclusively confirmed as PCNSL by magnetic resonance images (MRI) of brain, on T1 weighted (T1WI) and T2 weighted images (T2WI) and also on contrast-enhanced T1WI (Figure 2a; axial and 2b; coronal) intensely enhancing thalamic (arrows; a) and right skull base (arrow; b) lesions. Diffusion weighted image (DWI) and apparent diffusion co-efficient (ADC) map of brain revealed diffusion restriction and MR spectroscopy revealed elevation of choline peak characteristics of PCNSL. Findings of neuroimages, conclusively of lymphomatous characteristics suggested PCNSL. Ultrasound guided FNAC from the soft tissue mass at right skull base revealed non-Hodgkin’s lymphoma (Figure 3). The patient with clinicopathologically correlated profiles was diagnosed as a case of primary central nervous system lymphoma of non-Hodgkin’s type with rapidly progressive major cognitive dysfunction. The patient was treated with chemotherapy (CHOP) regimen consisting of injections;
cyclophosphamide 600 mg, vincristine 1 mg and dexamethasone 6 mg for 4 cycles, each at two weeks interval. The patient, on follow up, showed clinicoradiologically evident marked improvement. Clinically, cognition with MMSE score of 20/30 and memory improved markedly. Radiologically, MRI brain, repeated 8 weeks later revealed significant resolution and reduction in the size of the lesions with complete resolution of perilesional edema (Figures 4a and b).

Discussion

PCNSL is a rare, extranodal non-Hodgkin’s lymphoma which arises in and confines to CNS. In different studies, it accounts for 1-7 % of all primary CNS malignancies and 1 to 2 % of all lymphomas. Secondary CNS involvement is seen in 10% of systemic lymphoma. Recent studies reported an increasing trends in the incidence both in immunocompromised and immunocompetent subjects. This is attributed to increased incidence of AIDS, longer survival of AIDS patients because of availability of highly active antiretroviral therapy (HAART) and increased organ transplants in immunocompromised, and availability of better diagnostic modalities and greater clinical and neuropathological awareness in immunocompetent subjects. However, studies from India and few from abroad did not report any increase in the incidence of PCNSL despite increased incidence of AIDS. This is attributed to early deaths of AIDS patients due to opportunistic infections. Studies from India described clinical presentation of PCNSL in frequency of common occurrence but rarely as major cognitive dysfunction. We describe an individual case of PCNSL as a rare and unusual presentation of rapidly progressive cognitive dysfunction. We found clinicopathoradiological correlation in our patient consistent with profiles reported in different studies, interestingly those from India. Risks of PCNSL are increased in immunocompromised, occurs in 2-10% of AIDS patients where Ebstein-Barr virus is associated with oncogenesis leading to virally encoded expression of oncogenes. Genetically, PCNSL exhibits deletion on chromosome, 6q 22-23 or reduced expression of RPTK gene. PCNSL occurs in 03 to 87 years of ages, most frequently in 20-40 years, rarely above 60 years and earlier in immunocompromised subjects with 2:1 male to female incidence and more (7:3:1) in AIDS patients. Headache, weakness, paresis, vomiting, seizures, altered sensorium and behavioral changes are most frequently observed symptoms in PCNSL. Frontal and parietal lobes are most commonly

Fig. 1a and b: Axial NECT head revealed (a) hypodense lesions in bilateral thalamic regions (arrows) with perilesional edema (arrowheads) and (b) a soft tissue density lesion at right skull base (arrow) suggestive of primary central nervous system lymphoma (PCNSL)

Fig. 2a and b: MRI of brain on contrast-enhanced (a) axial and (b) coronal T1WI revealed thalamic (arrows; a) and right skull base (arrow; b) lesions, conclusively confirming primary central nervous system lymphoma (PCNSL)

Fig. 3: FNAC from right skull base mass lesion revealed non-Hodgkin’s lymphoma (primary central nervous system lymphoma; PCNSL). Note; characteristic intermediate to large lymphoid cells (arrows) and interspersed in the background small mature lymphocytes (arrowheads) and numerous lymphoglandular bodies (Giemsa stain)
involved supratentorial sites followed by multiple sites, whereas periventricular, ventricular and infratentorial sites are least involved. On neuroimaging in PCNSL, CT can depict isodense, hypodense or hyperdense lesions with haemorrhages and necrosis, MRI depict iso- to hypointense lesions on T1WI and T2WI, hyperintensities on FLAIR sequences and diffusion restriction on DWI and ADC map. MR spectroscopy reveals increased choline and decreased NAA peak. FDG-PET scan and T1-SPECT depict hypermetabolism in PCNSL than hypometabolism in other primary CNS tumors and metastases. MRI of brain is of key importance in differentiating PCNSL from toxoplasmosis, glioblastoma, abscess, progressive multifocal leukoencephalopathy and demyelination. Histologically, PCNSL is non-Hodgkin’s lymphoma most frequently occurs as diffuse large B-cell lymphoma (DLBCL) and most frequently occurs as diffuse large B-cell lymphoma, which reveals angiocentric pattern. On immunohistochemistry (IHC), immunophenotyping are performed by leucocyte common antigen (LCA), CD20 as B-cell marker and CD3 as T-cell marker. Our patient, 76 years elderly male and immunocompetent presenting as headache, most frequently occurring symptom and rapidly progressive cognitive dysfunction, a rare presentation with multiple sites involvement intracranially and extracranially in craniospinal axis, uniquely one at the skull base (Figures 1 and 2) facilitating FNAC, though stereotactic brain biopsy is recommended, for tissue diagnosis, represented a rare and unusual presentation of PCNSL. On neuroimaging, characteristic lymphomatous lesions suggestive of PCNSL were confirmed as non-Hodgkin’s lymphoma on cytology (Figure 3). We could not do the immunophenotyping as B cell or T cell lymphoma because of non availability of IHC facilities. Systemic lymphoma was evidently ruled out, therefore bone marrow was not done in our patient. Though, our case was a rare and an unusual presentation of PCNSL but we demonstrated clinicopathoradiologically correlated profiles, typical of PCNSL (Figures 1 to 4) similar to other studies. Treatment for PCNSL consists five, 14-days interval cycles of induction chemotherapy with methotrexate, procarbazine and vincristine (MVP). High dose methotrexate based polychemotherapy is the mainstay of the treatment. Whole brain radiotherapy (WBRT) with standard dose of 45 Gray in partial response and reduced dose of 23.4 Gray in complete response after Chemotherapy in 25 fractions for 5 weeks in each is recommended. Consolidation chemotherapy consists of 2 cycles of injection cytарибine 3 gm/m2/ day IV for 2 days. Targeted therapy and autologous stem cell transplantation are newly developed treatment modalities and are need of the hour. Our patient received 4 cycles of guarded chemotherapy consisting of cyclophosphamide, vincristine and dexamethasone, revealed clinicoradiologically evident (Figure 4a and b) marked improvement ascribing PCNSL as potentially reversible cause of major cognitive dysfunction. However, the prognostic factors determine the survival of the patient. The median survival is 17 to 45 months in immunocompetent and 3 months in immunocompromised subjects. Radiation and chemotherapy can improve 5 years survival to 20% to 30% from 7% with radiation.

Conclusion

PCNSL is a rare form of extranodal non-Hodgkin’s lymphoma and can have rare and unusual presentation as rapidly progressive cognitive dysfunction, potentially reversible following treatment. This necessitates the need for early and thorough evaluation of patients, particularly the elderly with dementia for PCNSL. This is well illustrated (Figures 1 to 4) in our PCNSL case report. However, the prognostic factors determine the survival of the patient.

References

Fatal Cutaneous Zygomycosis caused by Saksaenea Vasiformis

Vipul Patel¹, Viral Shah²

Abstract
Fungi in the class of zygomycetes usually produce serious infections in diabetics and immunocompromised hosts. Cutaneous zygomycosis is a less common form, with an unpredictable extent of anatomical involvement and clinical course.¹ Here, we report a case of primary cutaneous zygomycosis caused by saksaenea vasiformis as posttraumatic complications in a diabetic female. Zygomycosis was suspected and specimens from the surgical debridement were examined by microbiological and histopathological studies for conforming the clinical diagnosis. Rapid diagnosis, liposomal amphotericin B, and proper debridement of affected tissue are necessary to avoid a fatal outcome.

Introduction
Primary cutaneous zygomycosis is an uncommon infection caused by saprophytic fungi of the order mucorales which occurs most often in diabetes, burns and in immunocompromised patients.² Cutaneous infection account for 16% of all forms of zygomycosis with associated mortality of 16%, compared to 67% for rhinocerebral, 83% for pulmonary and 100% for disseminated infections.¹ Here we report a case of primary cutaneous mucormycosis caused by Saksaenea vasiformis in diabetic patient.

Case Report
A 60 year old female patient had history of injury over right foot fingers before 2 and 1/2 months. She is a known case of hypertension and diabetes since 10 yrs. After injury she gradually developed fever and blackening of Right toes and fingers. Patient was admitted in local hospital and investigations were Haemoglobin: 13.2 gm/dl, Total WBC count 11,500 / cumm with 88% polymorphs, Platelet count: 2,07,000, HbA1C: 7, RBS: 99, Serum creatinine: 0.74 mg/dl, Peripheral smear negative for malarial parasites. Patient gradually become septic in a 24 hours, so immediate amputation of 3 fingers done.

After 2 days of amputation Right lower limb arterial Doppler done which was suggestive of intimal thickening and calcification in major arteries of lower limb. After 4 days of 1st surgery lab investigations were: Hb: 13 gm/dl, Total WBC count increase to 15,300 with 87% polymorphs, Platelet count : 1,55,000, Creatinine : 0.69. After 5 days of amputation, patient complaining of altered sensorium and shifted to higher centre.

On presentation to us she had fever and altered sensorium. Started empirically higher antibiotics (Meropenem and Daptomycin) and investigations done. Complete blood investigations, blood culture aerobic and anaerobic, culture for bacteria and fungus, USG of abdomen, 2D ECHO were done. Hb:12.5 gm/dl. Total WBC count was 17,600 with 88% polymorphs, Creatinine: 0.62. Peripheral smear negative for malarial parasites. HIV and HBsAg were negative, CPK total 54. Pus for fungus culture and blood culture were negative. Pus for pyogenic culture showed the growth of pseudomonas aeruginosa and antibiotics continued as per the sensitivity pattern for 10 days.

Day by day patient’s clinically condition worsened with increase blackening of foot. So, Right foot below ankle amputation was done and patient kept in ICU for further management.

Post right foot below ankle amputation her condition got worsened over a three days of time. So advised for the right below knee amputation and sent necrosed tissue (Figure 1) for the Histopathology and fungal culture and Empirical Liposomal amphotericin B started.

KOH preparation of tissue suggests broad non septate hyphae resembling to mucormycosis. Histopathology is also favouring of mucormycosis. After few days, fungal culture grown white fluffy growth having no sporulation. Agar culture block was done for inducing sporulation. LPCB from Agar culture done (Figure 2) which was suggestive of saksaenea vasiformis.

Liposomal amphotericin B given for 14 days Diabetes was managed with insulin. CBC, renal and hepatic function, electrolytes were normal. After 14 days, patient discharged with Haemodynamically stable condition. Patient was followed up regularly and during his last visit, the site was found to have healed well and there was no evidence of any recurrence.

Fig. 1: Grossly infected part of leg

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Received: 28.02.2017; Accepted: 25.10.2019
Zygomycosis is a serious and fatal infection seen in immunocompromised individuals. It is caused by fungi belonging to class zygomycetes, order mucorales. The genera reported to cause invasive infection are Absidia, mucor, rhizomucor, rhizopus, Apophysomyces elegans, saksaenea vasiformis, Cunninghamamella, syncephalastrum. These fungi are ubiquitous in environment.³

Several clinical types of mucormycosis have been described-rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated forms. The cutaneous form is further divided into primary and secondary types. The rhinocerebral form is the most common and fulminating form seen commonly in diabetics with ketoacidosis. Rhizopus arrhizus is the most common species isolated from patients in a ten-year study of mucormycosis in India. The primary cutaneous form is the least common and the primary cutaneous mucormycosis caused by Saksenaea vasiformis manifests as bullous and necrotic lesions within a few days of traumatic injury due to potential contamination of wound with dust or soil. Mucormycosis can also manifest as Zosteriform lesions with the lesions resembling superficial granulomatus pyoderma and bull’s-eye cutaneous infarcts.

Mucormycosis caused by Saksenaea spp. most often occurs after traumatic implantation of the fungus with contamination with soil, but can also be due to inhalation of spores, tattoo, spider bites, insect stings, and the use of indwelling catheters.³ Systemic risk factors are diabetes, malignancy, leukopenia and immunosuppressive therapy.³

Key features of saksaenea vasiformis are flask shaped sporangia, failure to sporulate on primary isolation media. Sporulation can be induced by water culture technique. Colonies are fast growing, white with no pigment on reverse. Hyphae are broad, aseptate and sporangia are flask shaped with distinct spherical centre and long neck arising singly or in pairs from dichotomously branched daily pigmented rhizoids, columella are dome shaped and sporangiospores are small, oblong and are discharged through neck after apical plug.⁴

Successful treatment of cutaneous mucormycosis requires a combination of surgical debridement, antifungal therapy and medical management of the underlying predisposing condition. Amphotericin-B in both the conventional and liposomal forms has been used successfully to treat zygomycosis. The liposomal form can achieve higher concentrations of the drug without causing nephrotoxicity. One in vitro study comparing the activity of posaconazole, itraconazole, voriconazole, fluconazole and amphotericin-B on 31 isolates of zygomycosis showed that the mean inhibitory concentration (MIC) was lowest for Amphotericin-B and second lowest for posaconazole.

To conclude, Saksenaea vasiformis is increasingly being reported as a cause of subcutaneous zygomycosis. Cutaneous zygomycosis generally has a favourable outcome, zygomycosis due to Saksenaea vasiformis has also been reported to have a favourable outcome after treatment in most of the cases, hence when a zygomycetes species which fails to sporulate on routine media is isolated, the isolate should be cultured on nutritionally deficient media to induce sporulation so as to enable quick identification and to start treatment properly.

References
Mycotic Aneurysm of Brachial Artery in Case of Aplastic Anemia

Pritish Chandra Patra¹, Archana Srivastava², Hira Lal³, Rajesh Kashyap⁴

Abstract
Pseudo-aneurysm of the brachial artery is relatively rare condition affecting the arterial vessels of the limbs. It can be due to trauma, infections or systemic vasculitis. We report a patient with aplastic anaemia who developed pseudo-aneurysm of the brachial artery following an episode of bacterial sepsis. Methicillin resistant Staphylococcus aureus (MRSA) was isolated on blood culture. Patient was treated with systemic antibiotics and underwent embolization of the pseudo-aneurysm. He later developed vascular insufficiency of the forearm and a stent had to be placed in the brachial artery at the site of calcified thrombus inside the pseudo-aneurysm to produce the patency of the artery and ensure adequate blood flow to forearm and hand.

Introduction
An aneurysm is a localized dilatation of the blood vessel wall which is filled with blood. A true aneurysm involves all the three layers of the arterial wall. In contrast a pseudo-aneurysm is a collection of blood leaking completely out of an artery following a break in the integrity of it wall and is confined next to the vessel by a single wall of fibrous tissue. Mycotic aneurysis is a pseudo-aneurysm that results from an infectious process that involves the arterial wall. Brachial artery aneurysism is relatively rare when compared to lower extremity aneurysm with an incidence of 3-4%. We present the case of a young male with aplastic anemia who developed mycotic aneurysm of brachial artery following an episode of bacterial sepsis. The challenges encountered in the management of this condition are discussed in this case report.

Case Report
A 19-year old male diagnosed case of severe aplastic anaemia (SAA) treated with combination of antithymocyte globulin (ATG) and cyclosporine presented to the hospital with complaints of lower backache and fever for 10 days. On general physical examination the patient was febrile for 10 days. On general physical examination the patient was febrile and had pallor with tenderness and spasm over the lumbar para-splinal area bilaterally. Laboratory investigations revealed haemoglobin level 5.9 g/dl, total leukocyte count (TLC) 1.3 X 10⁹/l (differential count 52% polymorphs, 46% lymphocytes and 2% monocytes) and platelet count of 50X 10⁹/l. Methicillin resistant Staphylococcus aureus (MRSA) sensitive to clindamycin and vancomycin was isolated on blood culture. Magnetic resonance imaging (MRI) of sacro-iliac joint revealed an abscess near the left sacroiliac joint with mild joint effusion. The patient was treated with parenteral vancomycin and received packed red blood cell (PRBC) and random donor platelet (RDP) transfusions for management of low haemoglobin and platelet counts. The infection resolved after four weeks of antibiotic therapy and repeat blood cultures on two occasions were sterile.

On follow-up one month later the patient presented with a swelling on the medial side of the left arm which was progressively increasing in size but no functional impairment of limb. Physical examination revealed an ovoid swelling measuring 5 x 3 centimetre (cm) in size on the medial aspect of left arm, approximately 15 cm above medial epicondyle of humerus. No visible pulsations, scar marks, pigmentation or prominent veins were seen over the swelling. Palpation revealed a 5x3 cm non tender, pulsatile, non-expansible, non-fluctuant, compressible but non-reducible mass. It was not attached to the adjacent skin, muscles or bone.

Swelling was more mobile in horizontal plane than in longitudinal plane. No bruit was audible over the swelling and surface temperature was normal. There was no neurovascular deficit and the systemic examination was normal.

Ultrasoundography of proximal left arm swelling showed a pseudoaneurysm arising from left proximal brachial artery measuring 5 x 3 x 2 cm in dimension with peripheral thrombus formation. Neck was narrow and measured 4-5 mm. Proximal and distal brachial artery appeared normal. CT angiogram was done which revealed a pseudoaneurysm arising from left brachial artery (Figure 1). A diagnosis of mycotic pseudo-aneurysm of the left proximal brachial artery was made. In view of low platelets counts he was planned for embolization of the pseudo-aneurysm. A 5 mm x 20 mm balloon (Cook Medical, Bloomington, IN, USA) was advanced over 0.18 inch micro-guidewire (Transend®; Boston Scientific, Boston, MA, USA) through a 6F guider catheter (Envoy; Cordman, MA, USA) placed in the left subclavian artery. The balloon was inflated across the neck of the pseudo-aneurysm and angiogram taken which reveal no filling of aneurysm suggestive of complete neck occlusion. Under ultrasound guidance the pseudo-aneurysm was punctured percutaneously with inflated balloon across the neck of pseudo-aneurysm and 2 ml thrombin (5000 U; GenTrac, Inc) was injected in the pseudo-aneurysm sac. Balloon was kept inflated across the neck for 30 minutes to achieve complete thrombosis of the pseudo-aneurysm sac. After 30 minutes balloon was deflated and check angiogram was taken from left subclavian artery which showed partial filling of pseudo-aneurysm sac. Again balloon was inflated across the neck of pseudo-aneurysm and 3 ml NBCA (N-butyl cyanoacrylate glue) was injected in the sac in a dilution of 25%.
with lipiodol (LIPIODOL® (ethiodized oil); Guerbet; USA) percutaneously. Again the balloon was re-inflated and checks angiogram taken which showed mild to minimal filling of pseudo-aneurysm sac. Balloon was re-inflated and kept in situ for 24 hours. After 24 hours balloon was deflated, wire and balloon catheter was removed. Check angiogram showed non filling of residual aneurysm sac with adequate distal blood flow.

Three months later the patient present with pain in the left forearm and fingers and wasting of forearm and hand muscles. On examination the mass in the proximal arm was hard, non-tender and non-compressible. The skin of the forearm and palm revealed decrease temperature and there was wasting of flexor muscles of forearm and palmar muscles of hand. The left radial artery was feeble. Repeat USG revealed calcified thrombus in the region of brachial artery pseudo-aneurysm sac with decreased distal blood flow. The patient underwent arterial catheterization and a stent was placed in the brachial artery (Wall Stent©; Boston Scientific; MA, USA) to ensure adequate distal blood flow. The patient showed clinical improvement with amelioration of his symptoms and signs of vascular insufficiency. A plain radiograph of left upper limb with chest showed a calcified thrombus with the stent-in-situ. (Figure 2).

Discussion

Arterial aneurysms of the upper limb are rare. Brachial artery is the most frequently affected vessel with an incidence of 3-4%. Brachial artery aneurysms can be true or false. True aneurysms occur mainly due to atherosclerotic process, repetitive trauma, congenital disease, inflammation or can be idiopathic. Pseudo-aneurysms have become more frequent because of the increasing application of invasive procedures like arterial line insertion, cardiac catheterization and renal dialysis access procedures. They can also occur due to infections and are called mycotic aneurysms.

Several mechanisms have been postulated in the pathogenesis of mycotic aneurysm due to anyone of the following mechanisms: (1) dissemination of emboli from the infective endocardial vegetation of native or prosthetic cardiac valve; (2) direct bacterial inoculation of the arterial wall following trauma; (3) infection of pre-existing aneurysm; (4) hematogenous or lymphatic spread of infection from local purulent focus or systemic bacterial sepsis. The clinical presentation of a pseudo-aneurysm is variable. It usually presents as a slow developing painless, pulsatile and asymptomatic mass and may take days to months, even years to manifest clinically. Occasionally, complications such as haemorrhage or thrombosis occur causing the mass to grow rapidly and become painful producing vascular insufficiency with ischemic changes in the anatomical regions supplied by it.5

Selective arteriography is the gold standard radiological investigation for evaluation of arterial aneurysms. Computerized tomography with angiography (CTA) is more preferred as it allows reconstruction of three dimensional reconstruction images of the vascular anatomy which is helpful for surgical and endovascular therapeutic procedures. Contrast enhanced magnetic resonance imaging (MRI) with angiography is useful for evaluation of aortic and cerebral artery aneurysms. Doppler ultrasound is used for the initial evaluation of aneurysms of the peripheral arteries.6

The treatment of brachial artery aneurysm depends on the location, size, pathogenesis, and accessibility of the pseudo-aneurysm.7 Mycotic brachial artery aneurysm has been treated surgically by proximal ligation and resection of the aneurysm. Arterial reconstruction has been done either by end to end anastomises, vein graft interposition or vein graft. Endovascular methods (endovascular stent-graft implantation, embolization of sac, embolization of distal and proximal arterial segments) have become more popular because they are less invasive and associated with lower complication rates. In our patient, we preferred endovascular intervention due to presence of pancytopenia corollary to aplastic anemia and reduce the risk of complications associated with surgery.

References

Central Visual Process- Hubel & Weisel

Jayant Pai-Dhungat¹, Geeta Gore²

David Hunter Hubel (1926-2013) & Canadian American neurobiologist & Torsten Nils Weisel (born 1924) a Swedish American neurobiologist shared half of the 1981 Nobel Prize for Physiology or Medicine for their collaborative effort concerning information processing in the visual system.

David Hubel attended McGill University in Montreal and received his MD in 1951. He held positions at the Montreal Neurological Institute, and in 1959, joined the faculty of Harvard Medical School along with Torsten Weisel.

Torsten Weisel was born in Uppsala, Sweden, and received his medical degree in 1954. Weisel moved to the United States to work at Johns Hopkins University School of Medicine, to begin his fellowship in Ophthalmology (1955). He met David Hubel in 1959, beginning a long collaboration. In 1959, Weisel and Hubel moved to Harvard University and began research collaboration for studying visual occipital cortex.

In an experiment done in 1959, they inserted a microelectrode into primary visual cortex of an anaesthetized cat, and projected patterns of light and dark lines in front of the cat. Duo found that some neurons fired rapidly when lines presented at an angle, while others responded best to another angle. Some of these neurons responded to light pattern and dark patterns differently. Hubel and Weisel called them simple cells. Still other neurons, which they called complex neurons, detected edges regardless of where they were placed in the receptive field of neurons, and preferentially detected motion in certain directions. Their studies showed how the visual system constructs complex representation of visual information from simple stimulus. Major transformation occurs as cells from one layer feed into another layer of striate cortex. Signals are processed by visual neuronal groups into neocortex to generate edge detectors, motion detectors, stereoscopic depth detectors, color detectors and object identity. They form building blocks of the visual scene (processing modules).

Hubel & Weisel also showed by depriving kittens from using one eye and showed that columns in the primary visual cortex receiving inputs from other eye took over the areas that would normally receive inputs from the deprived eye. This has important implications for the understanding of deprivation amblyopia, a type of visual loss due to unilateral visual deprivation during the critical period of development. These kittens also did not develop areas receiving inputs from both eyes, a feature needed for binocular vision. Duo’s experiments showed that ocular dominance develops irreversibly, early in the child development. These studies helped in understanding treatment of childhood cataract and strabismus.

Central visual pathway is extremely complex system in the human brain. The optic tracts extend to the two lateral geniculate nuclei (LGN) in the thalamus, which act as relay stations to primary occipital visual cortex. Puzzling feature of LGN is that only 20-25% of the axons reaching them come from the retina. The remaining 75-80% descends from the cortex or other parts of the brain and process vivid details of the world; color, motion, depth and meaning that impinge on human consciousness. Internal images are the product of extraordinary amount of processing; involving roughly half the cortex and this processing does not follow a simple unitary pathway.

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Over-coming Challenges in Conducting Post-graduate Practical Examination during COVID -19 Pandemic

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Sir,

On 24 March 2020, Government of India, as a part of covid-19 preparedness, announced a nationwide lockdown for 21 days which has been subsequently extended till May 31, thereby limiting movement of the entire population. Under this situation Medical education system across the world is also facing major difficulties conducting end of curriculum summative assessment of various Under and Post Graduate Courses. Although various applications of digital mode and various web based platform have been in the rise in the last decade for teaching learning activities as well as formative assessment in field of Medical Education. However, a sudden transition to adopt this method for summative assessment to determine the attainment of desired level of competency in a postgraduate of a Medical school is indeed a challenging task. It is also the responsibility of administrators and Faculty to ensure availability and facilitation of suitable process even under such pandemic conditions for a timely completion of Course keeping in mind the uncertainties ahead.

At this time point, there is scant guidance for medical educators on an alternative approach for practical examination for summative assessment. Therefore, stakeholders in Institute discussed and decided to adopt an innovative idea of conducting real time online practical examination with external examiners in a remote site.

The challenges included:
1. Non availability of clinical material (Real patients as long case and short cases)
2. Maintaining social distancing norms while conducting exams
3. Non availability of external examiners due to movement restrictions
4. Assessing all domains of Accreditation Council for Graduate Medical Education (ACGME).

External examiners were informed about the change in mode of exam, virtual material and evaluation system via videoconferencing. Blueprinting of practical examination and all examination related material was shared with the examiners. Assessment module was designed in so as to test all the six domains (Patient care, Medical knowledge, Professionalism, Interpersonal and Communication skills, Practice-based Learning and Improvement, and Systems-based practice) of ACGME. Examination was conducted over 2 days and was subdivided into two main parts- Objective Structured Clinical Encounter (OSCE) and Objective structured long examination record (OSLER). This was done without compromising the safety of all participants, minimising risk and most essential maintaining the sanctity of examination.

The following key principles were applied throughout:
- Strict infection control and personal hygiene; use of face masks, hand sanitisation
- Social distancing of individuals
- Use of simulated patients for demonstration of clinical skills
- Google meet facilitated evaluation of candidates by external examiners
- No large group gatherings

A well ventilated seminar hall was chosen as the venue. Two external examiners from two different Institutes of national importance were in the examination board to conduct and supervise the practical examination over the online video platform. A mixed model approach was followed, in which both the internal (real) and external (virtual) examiners were involved in assessment. OSCE examination was accomplished with virtual case scenarios and high fidelity mannequins’ which were provided by the Advanced Skills Lab of our Institute. The Information and Technology division assisted for an interrupted internet connection during the entire examination with a dry run to check and ensure connectivity one day before in the venue site. While postgraduates performed the External Examiners supervised online with help of Laptop available in front of stations.

Non availability of real patients was a real challenge in conducting OSLER. To compensate for real patients 20 detailed case summaries of patients and 10 short clinical encounter summaries were prepared and shared with the external examiners 3 days before the actual exam. The case summaries included detailed history and clinical examination findings of real patients admitted in ward previously. Case histories were allotted to candidates by lucky draw system under direct supervision of the external examiner. Students were given one hour to prepare detailed case summaries so as to develop a diagnosis and management plan of that virtual patient. Each candidate subsequently presented case summaries and were evaluated by examiners, both real and virtual, on the basis of preformed checklist shared with all the examiners. A simulated patient was kept in examination hall to assess examination skills of the candidates.

In feedback, examinees felt that the assessment was objective and less stressful and examiners felt that online assessment was time and cost saving. However, they felt real patients would have been better to evaluate the affective skills of the candidate.

Computer-based testing in high-stakes examining in higher education has developed rather slowly due to institutional barriers and teacher and student reluctance, but in today’s scenario this seems to be the best way to conduct examinations. We hope that we have paved the wave for others to follow this examination pattern and by customizing it to their requirement this examination system can continue in future in situations as applicable even after this COVID pandemic is over.

References

“COVID 19” - A New Baby in the Family of Viruses Causing Arthropathy: Don’t Overlook it can be First Manifestation of Severe COVID Infection

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Sir,

Whenever we talk about novel corona virus, clinical presentation which comes across our minds is either of influenza like illness or severe acute respiratory syndrome. Now it has been eight months since we are battling this pandemic, and as we are becoming more friendly with this deadly virus our vision has also broadened and now, we seeing myriads of presentations apart from ILL and SARI. A 45-year-old male presented to us with complaint of sudden onset pain, swelling, redness and stiffness in left knee joint for one day. Two days later patient developed high grade fever. There was no prior history of arthritis in the past. There was no history of trauma, low back pain, psoriasis, Urinary tract infection, diarrhea, Inflammatory bowel disease, hypertension, diabetes, oral or genital ulcers. Since patient was in a habit of taking beer on daily basis, a suspicion of unusual presentation of gouty arthritis made. On examination Temperature was 102 degrees with infrared thermometer, Pulse rate was 102/min, respiratory rate was 24 / min and rest vitals, saturation, general and systemic examination were normal. Musculoskeletal examination revealed fullness in suprapatellar fossa, fluctuation present, erythema and joint margin tenderness present. Biochemistry revealed high TLC (14,300 cells/ mm³), predominant neutrophils 89%), ESR 37 mm/hour and CRP 67.8 mg/dl (normal < 6 mg/dl). USG (Musculoskeletal) done, it only showed suprapatellar collection of synovial fluid, no evidence of crystals. Synovial aspiration was planned, so rtPCR for nCoV was sent which came out to be positive with Ct 10/40. Synovial aspiration done with full covid precaution, and aspirate revealed inflammatory finding with no evidence of crystals, and gene expert negative for M. tuberculosis or corona virus. On further evaluation Ferritin was 999.9 ng/ml (normal 30-220 ng/ml in males), S.LDH was 332.26 u/l (normal 240-480 u/l), S. Procalcitonin 0.04 ng/ml (< 0.5 ng/ml), D- Dimer 560 ng/ml (normal 12-150 ng/ml). HRCT thorax revealed atypical pneumonia suggestive of viral aetiology. So, on the basis of above findings diagnosis of acute monoarthrosis with B/L consolidation cause viral pneumonia cause COVID 19 was made.

References

Morbidity Among Home Isolated COVID-19 Patients

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Sir,

First case of COVID 19 was detected in our country on 30th January 2020.1 More than 10.395 million cases have been confirmed in India as on 7th January 2021, out of which more than 150000 have succumbed to the disease.2 Govt of India released guidelines advising home isolation for patients presenting with very mild to mild symptoms, pre-symptomatic and asymptomatic cases.3 Elderly patients aged more than 60 years and those with co-morbidities such as hypertension, diabetes mellitus, heart disease, chronic lung/liver/ kidney disease, crebro-vascular disease, etc. could only be allowed home isolation after proper evaluation by the treating medical officer. Patients and/or caregivers had to report to the nearest available medical facility if there was breathlessness, fall in oxygen (O2) saturation, persistent chest pain, etc. in states which have only limited hospitals catering to corona care, advising home isolation could be fraught with dangers.

Table 1: Characteristics of covid 19 patient

<table>
<thead>
<tr>
<th>Variable</th>
<th>Covid symptoms (n=150)</th>
<th>Post covid symptoms (n=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>97 (64.66)</td>
<td>48 (32)</td>
</tr>
<tr>
<td>Fever</td>
<td>77 (51.33)</td>
<td>13 (8.66)</td>
</tr>
<tr>
<td>Cough</td>
<td>52 (33.33)</td>
<td>15 (10)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>32 (21.33)</td>
<td>0</td>
</tr>
<tr>
<td>SOB</td>
<td>8 (5.33)</td>
<td>10 (6.66)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0</td>
<td>13 (8.66)</td>
</tr>
<tr>
<td>Loss of Taste</td>
<td>15 (10)</td>
<td>2 (1.33)</td>
</tr>
<tr>
<td>Loss of smell</td>
<td>11 (7.33)</td>
<td>0</td>
</tr>
<tr>
<td>Generalised body pain</td>
<td>3 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>Weakness</td>
<td>13 (8.66)</td>
<td>20 (13.33)</td>
</tr>
<tr>
<td>Tiredness</td>
<td>7 (4.66)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Age &gt;60</td>
<td>12 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Male</td>
<td>116 (77.33)</td>
<td>0</td>
</tr>
<tr>
<td>Diabetic</td>
<td>15 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Antigen test</td>
<td>89 (59.33)</td>
<td>0</td>
</tr>
<tr>
<td>RTPCR</td>
<td>82 (54.66)</td>
<td>0</td>
</tr>
<tr>
<td>Require hospitalisation</td>
<td>25 (16.66)</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>2 (1.33)</td>
<td>0</td>
</tr>
</tbody>
</table>

Bed availability when required is still a major concern for corona patients. Till date no audit has been done to assess the population characteristics who have been advised home quarantine. It is important to know their clinical presentation, proportion of ultimately requiring hospitalisation and their after recovery. This study was performed with aim to identify these clinical characteristics and main symptoms of patients advised home isolation. Secondary objectives were to know what proportion of patients required hospitalisation and what proportion of patients had residual symptoms after recovery.

We tabulated a list of all patients advised home quarantine as on 1st week of July across the various health centres of Patna. It was a cross sectional telephonic survey of 150 patients including 34 females and 116 males. We called 163 patients, out of which 10 did not agree to participate in the survey. There were 3 wrong numbers provided. All of the patients who responded, had completed home isolation for at least 14 days. We noted the clinical presentation at time of confirmation of covid infection, symptoms during isolation, as well as any residual or new symptoms after recovery.

After describing the survey and obtaining verbal consent for participation in the survey, patients were asked all questions. 64.66% patients were asymptomatic at the
time of diagnosis and they remained asymptomatic throughout their home isolation. Among symptomatic patients, fever was the most common symptom in 51.33% of patients at the time of diagnosis, followed by cough and sore throat in 33.33 percent and 21.33 percent respectively. Number of patients who ultimately required hospitalization was 16.66 percentage. According to us, this seems to be large figure probably highlighting either an improper selection of for home isolation or of health care facilities for these patients. Patients at higher risk of morbidity such as those above the age of 60 years had also been advised home isolation. This age group formed around 8 percentage of the total patients surveyed (Table 1). We also asked for any residual or new symptoms after 14 days of home isolation. Almost one third (32%) of patients continued to have some symptoms. 13.33% of patients complained of weakness. 8.66% had fever, 10 percent had cough and shortness of breath was complained by 6.66 percent of respondents (Figure 1). In this part of the world, most of the patients had been diagnosed by the rapid antigen test (59.33%), however some patients did go for both Antigen and RTPCR test. Most alarmingly, we noted two deaths of patients who had been advised home isolation.

Based on this survey, we believe that there is a need for more strict criteria to allow home isolation in the state of Bihar. After advising home isolation, there should be a robust way to track progress of these home isolated patients considering significant number of patients require hospitalisation. The criteria warranting immediate admission must be mentioned in a language that the patient and their relatives understand. Given the stigma attached with the disease especially in rural and poor populations, importance of adequate space at home for isolation should be ensured. In a resource poor population, if this cannot be ensured, institutional isolation would be better.

Table 1 Characteristics of home isolated COVID 19 patient

References

2. Indian COVID 19 Dashboard. [accessed 7 January 2021)], Available online: https://www.covid19india.org/

Fig. 1: Comparison of symptoms during covid and post-covid period

Y Axis represents number of study patients
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<td>Olmesartan Medoxomil 20/40 mg + Amlodipine 5 mg + Cilnidipine 12.5 mg Tablets</td>
<td>Olmesartan Medoxomil 10 mg + Micofenolate Mofetil 25/50 mg Tablets</td>
</tr>
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Stefano Omboni et al.; Management of arterial hypertension with ARBs: Current evidence and the role of olmesartan. Cardiovascular Therapeutics. 2018;36 e12471

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