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	INSTITUTIONAL		PERSONAL	
	Annual	Per Copy	Annual	Per Copy
Nepal	Nrs. 2000	Nrs. 1000	Nrs. 1000	Nrs. 500
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ISSN Print 2594-3367   ISSN Online 2631-2107

EDITORIAL

Osteoporosis, need for paradigm shift in Nepal health policy

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World Health Organisation (WHO) describes osteoporosis as a 'progressive systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture'.[1] Osteoporosis is frequently surveyed diagnosed and treated in developed nations for reason being increasing degenerative diseases among increased aged population. Among risk group of osteoporosis cohort one among three females (33%) and five males (20%) sustain fragility fracture in lifetime.[2] The cost of managing osteoporotic fracture is much higher than that of prevention.[3] Hence efforts are more focused to prevent the osteoporosis by developing evidence based guidelines and implementing as national policy.[4] The effective strategy for prevention of osteoporosis related burden are through fracture risk assessment, lifestyle measures and pharmacological interventions.[4]

Nepal is expected to have higher burden of osteoporosis with increasing geriatric population in coming decades. Preventive measures has to be implemented before aging population grow with osteoporosis and present to clinician with debilitating fractures and severe pain. Like developed nations these measures has to be implemented by training clinicians to keep low threshold to screen osteoporosis at early stage. Use of fracture risk assessment tool is highly cost effective and sensitive[5]

but validation of such tool in Nepalese population is due. Use of dual-energy X-ray absorptiometry (DXA), ultrasound and computed tomography after screening with fracture assessment tools has been recommended.[6] However clinical interpretations of the investigations and their feasibility at point of care are the challenges. Rampant use of steroids, thyroxine and proton pump inhibitors as over the counter drugs is likely to compound the burden of osteoporosis.[4] Besides well accepted culture of consuming alcohol and increasing popularity of habitual smoking among younger generation need to be intervened before the onset of osteoporosis. Current recommendation on life style measures are increasing the level of physical activity, stopping smoking, reducing alcohol intake to ≤2 units/day, and reducing the risk of falls and ensuring adequate dietary calcium intake and vitamin D status.[7] Effective life style measures demands motivation, multiple sessions of goal directed counselling, family and environmental support, self-help group and team work with internist, rheumatologist, metabolic endocrinologist, general practioner, geriatrician, psychiatrist, psychologist, orthopedics, and physiotherapist.[5] These measures has to be roll down in policy level along with pharmacological interventions. All most all pharmacological measures are available at urban set up in Nepal. The impact of pharmacological agents requires at least use for a few years. This could compromise compliance by asymptomatic and mild symptomatic patient the target group for preventive strategy. Health insurance can address the cost of non-pharmacological and pharmacological cost in sustainable form.

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Periodontal Health Status and its Impact on the Quality of Life among Diabetics attending Medical and Dental Out Patient Departments of a Tertiary Care Center of Nepal

Bhagat T[1], Shrestha A[1], Rimal J[2], Maskey R[3], Agrawal SK[1], Gautam U[1]

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Abstract

Background: Diabetics are more prone to periodontal diseases leading to poor oral function affecting their quality of life. The objective of the study was to assess the impact of periodontal health on the quality of life among diabetics using the short version of the Oral Health Impact Profile (OHIP -14). **Methods:** It was a descriptive cross-sectional study. Data was collected using translated and validated Nepalese version of OHIP-14 questionnaire and clinical examination for periodontal status (Community Periodontal Index and Loss of Attachment index) was done using mouth mirror and World Health Organization probe under natural light. Data was entered and analyzed using SPSS version 11.5. Mann-Whitney U test and Kruskal-Wallis tests were used to compare OHIP-14 scores between genders and periodontal status respectively. Statistical significance was established at p<0.05. **Results:** One hundred and forty-five subjects with confirmed diabetes participated in the study. Overall, 41% were male participants were as 59% were females. Majority of the participants had calculus with CPI score 1 (n=131, 90.3%) and another majority had loss of attachment 3-5 mm with LOA score 1 (n=55, 37.9%). There was no significant difference in mean scores between two genders (p=0.231). The OHIP scores among participants with highest CPI and LOA scores had statistically significant difference (p=0.011 and p=0.006 respectively). **Conclusions:** Periodontal status was poor among diabetics with significant impact on their oral health related quality of life. Glycemic control along with periodontal maintenance is required to enhance quality of life among such patients. This might be possible with comprehensive medical approach for diabetic patients.

Keywords: Diabetics, Periodontal health, Quality of life

Background

People suffering from diabetes mellitus are more prone to periodontal diseases especially deep periodontal pockets and gingival recession which in turn leads to functional limitation. As the patients are unable to chew properly their general health is also impaired leading to poor quality of life. Diabetes mellitus is a major public health problem today. There is bidirectional relationship between periodontal disease and diabetes mellitus. Periodontal disease is considered as a common complication as well as a possible risk factor for poor metabolic control.[1] Diabetes Mellitus with its concomitant oral manifestations especially in the form of periodontal disease not only affects people physically but also has emotional and psycho-social consequences.[2,3]

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Recent literatures have tried to explore, in a broader perspective, the relationship between various patient-centered outcomes of satisfaction factors and periodontal health.[4] This emphasis on Quality of life (QoL) is consistent with the concept that health is a resource and not simply the absence of disease.[5] Interest in the idea of 'quality of life' is growing rapidly. "Health-related quality of life" is a widely used concept employed for subjective assessment of an individual's health and quality of life issues. Regarding the relationship of health and disease to quality of life, there appears to be an association between these domains which is not clearly defined. Locker suggested that health problems may affect quality of life but such a consequence is not inevitable. Individual attitudes are not constant, vary with time and experience, and are modified by phenomena such as coping, expectancy and adaptation.[6] By definition, people who lose teeth are impaired (i.e., have lost a body part). Other less well documented consequences of tooth loss include disability like lack of ability to perform tasks of daily living such as speaking and eating. Similarly, minimizing social contact due to embarrassment with complete denture wearing can also be reported in the form of handicap.[7,8]

The objective of the study was to assess the periodontal health status of diabetics attending medical and dental out patient departments of B. P Koirala Institute of Health Sciences, a tertiary care centre in Dharan, Nepal and assess its impact on the quality of life using the short form version of the Oral Health Impact Profile (OHIP -14).

Methods
It was a hospital based cross-sectional study. The patients were interviewed using a self-administered questionnaire of OHIP-14. OHIP-14 is a 14-item questionnaire which covers seven domains of oral health impact: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap based on Locker's adaptation of the WHO's classification of disease-impairment-disability-handicap (Locker, 1988).[10] The number of questions in each domain has been reduced to two and the Likert response format (4 = very often, 3 = often, 2 = occasionally, 1 = hardly ever, never = 0) is used. Frequency of impacts is calculated by summing the reported negative impacts (i.e., very often/often or occasionally) across the 14 statements. Ethical approval for the study was obtained from Institutional Ethical Review Board (IERB), BPKIHS [Ref. Aca. 709/069/070]. Written consent was obtained from participants who were enrolled.

OHIP-14 is a valid measure for Oral Health Related Quality of Life (OHQRoL). A major advantage of this measure is that the statements are derived from a representative patient group, and were not conceived by dental research workers. The social consequences of oral disorders that are considered to be important by the patients can be can be better explored using such sophisticated measure of oral health. The measure has been used in a number of oral health impact studies globally.[9]

Oral examination was done using WHO (World Health Organization) probe and plane mouth mirror to measure the Community periodontal Index and Loss of Attachment.[11] One hundred and forty-five patients, diagnosed with diabetes, were enrolled from the hospital OPD (diabetic clinic) purposively. All the patients giving written informed consent were included in the study.

Data were entered into computer using excel and analyzed using SPSS 11.5. The values are expressed as mean and standard deviation for continuous variables and percentage for nominal variables. Mann-Whitney U test and Kruskal-Wallis tests were used to compare OHIP-14 score between gender and periodontal status respectively. Statistical significance was established at $p<0.05$.

Results
A total 145 participants were included in our study. The mean age of the participants was 50.7 years (SD 14). Majority of the participants were female (n=86, 59.3%).

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Periodontal examination for assessment using CPI and LOA revealed only one participant having healthy gingiva with no bleeding/calculus/pockets and 74 (51%) participants having no loss of attachment. Majority of the participants had calculus with CPI score 1 (n=131, 90.3%). Similarly, another majority had loss of attachment 3-5 mm with LOA score 1 (n=55, 37.9%). The periodontal status of the participants has been shown in detail in (Table 1).

Table 1: Periodontal status of participants (n=145)

Highest CPI score	
Condition (Score)	**Frequency (Percentage)**
Normal (0)	1 (0.7%)
Bleeding on probing (1)	131 (90.3%)
Calculus (2)	11 (7.6%)
Pocket depth 4-6 mm (3)	2 (7.6%)
Pocket depth 6 mm or more (4)	145 (1.4%)

Highest LOA score	
Condition (Score)	**Frequency (Percentage)**
Loss of attachment 0-3 mm (0)	74 (51%)
Loss of attachment 4-5 mm (1)	55 (37.9%)
Loss of attachment 6-8 mm (2)	9 (6.2%)
Loss of attachment 9-11 mm (3)	7 (4.8%)

The responses of individual participants to Oral Health Impact Profile (OHIP) questionnaire items has been shown in (Table 2). The internal consistency of the scale as measured by Cronbach's alpha was 0.898. Nearly 20% had painful aching in mouth, 14.5% felt uncomfortable to eat, 11.4% were self-conscious, 9.7% had to interrupt their meals, 3.5% felt tense, 5.5% felt difficult to relax, 2.8% had difficulty doing their jobs, 2.1% were unable to perform functions such as eating and speaking and 1.4% felt embarrassed.

Table 2: OHIP-14 responses of the participants

OHIP-14 questionnaire item	Responses to questionnaire [n (%)]				
	Never	**Hardly ever**	**Occasionally**	**Often**	**Very often**
Pronouncing words	124 (85.5%)	8 (5.5%)	11 (7.6%)	2 (1.4%)	0
Sense of taste worsened	119 (82.1%)	11 (7.6%)	13 (9%)	1 (0.7%)	1 (0.7%)
Painful aching (mouth, teeth)	81 (55.9%)	36 (24.8%)	23 (15.9%)	5 (3.4%)	0
Uncomfortable to eat any foods	117 (80.7%)	7 (4.8%)	18 (12.4%)	3 (2.1%)	0
Been self-conscious	127 (87.6%)	11 (12.8%)	26 (9%)	5 (1.7%)	2 (0.7%)
Felt tense	132 (91%)	8 (5.5%)	4 (2.8%)	1 (0.7%)	0
Diet been unsatisfactory	124 (85.5%)	14 (9.7%)	7 (4.8%)	0	0
Interrupt meals	124 (85.5%)	7 (4.8%)	11 (7.6%)	3 (2.1%)	0
Difficult to relax	133 (91.7%)	4 (2.8%)	6 (4.1%)	2 (1.4%)	0
Feel a bit embarrassed	137 (94.5%)	6 (4.1%)	2 (1.4%)	0	0
Irritable with people	136 (93.8%)	6 (4.1%)	3 (2.1%)	0	0
Difficulty doing usual jobs	132 (91%)	9 (6.2%)	4 (2.8%)	0	0
Life in general less satisfying	137 (94.5%)	7 (4.8%)	1 (0.7%)	0	0
Totally unable to function	134 (92.4%)	8 (5.5%)	3 (2.1%)	0	0

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Age and OHIP scores were found to have no significant association as shown by Pearson correlation r=0.046 (p=0.580). There was no significant difference in mean scores between two genders (p=0.231). The OHIP scores among participants with highest CPI and LOA scores had significant difference (p=0.011 and p=0.006 respectively) as shown in (Table 3).

Table 3: Comparison between OHIP-14 score and study variables

	OHIP score Mean (SD)	Mean rank OHIP score	p-value
Gender			
Male	2.24 (4)	68.24	**0.231**[a]
Female	3.4 (5.4)	76.27	
Highest CPI score			
Normal (0)	6 (0)	120	**0.011**[b]
Bleeding on probing (1)	2.5 (4.7)	69.42	
Calculus (2)	6.6 (5.5)	105.05	
Pocket depth 4-6 mm (3)	7 (8.5)	107.75	
Highest LOA score			
Loss of attachment 0-3 mm (0)	2.3 (4.8)	62.84	**0.006**[b]
Loss of attachment 4-5 mm (1)	3.2 (4.9)	79.54	
Loss of attachment 6-8 mm (2)	5.7 (6.3)	97.61	
Loss of attachment 9-11 mm (3)	4 (4.4)	97.43	

[a] Mann-Whitney U test
[b] Kruskal-Wallis test
Bold signifies statistical significance at p<0.05

Post hoc analysis with pair-wise comparison showed significant difference between sub-groups with Highest CPI 2 and Highest CPI 3 (test statistic: -35.626; p<0.004). Similarly, post hoc analysis with pair-wise comparison showed significant difference between sub-groups with Highest LOA 0 and Highest LOA 1 (test statistic: -16.699; p=0.018); and significant difference between sub-groups with Highest LOA 0 and Highest LOA 3 (test statistic: -34.591; p=0.027).

Discussion

This study found significant difference among mean OHIP scores and different CPI and LOA groups. The relationship between oral disease and quality of life has been demonstrated in various literatures.[12–14] Patient-oriented subjective measures like OHRQoL enhances the understanding of the relationship between oral health and general health and demonstrate to clinical researchers and practitioners that improving the quality of a patient's well-being goes beyond simply treating oral diseases.[15] Several studies have assessed impact of periodontitis on OHRQoL.[16,17] An association between clinically diagnosed periodontal diseases and subjectively assessed OHRQoL with a dose-response relationship has been demonstrated in various studies.18 Similarly, Cunha-Cruz et al.[19] showed that oral health-related problems in patients presenting to a periodontal specialist office negatively affect their quality of life. Individuals with severe marginal bone loss experienced worse quality of life compared with individuals with no/minor marginal bone loss in another study.20 The studies have assessed the association across different populations.[21] Clinicians have been recommended to use oral health assessment tools to determine individual treatment and approaches to promote the oral health of patients undergoing hemodialysis and improve their QOL.[4]

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ISSN Print 2594-3367   ISSN Online 2631-2107

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Our study employed a specific diabetic population to assess the effect of periodontal disease in quality of life and found significant relation among the same. Similar finding was reported in study by Rao et al[22] in Indian population where a significant impact of periodontal health on the quality of life among diabetics was demonstrated. DM associated with chronic periodontitis have shown to negatively affect QoL, even considering well-controlled diabetic patients.[23] Another study by Irani et al2, however, showed that DM does not impact on overall Oral Health Related Quality of Life (OHRQoL) when measured by OHIP-49. Our study, on the contrary, used shorter form OHIP-14. OHIP-14 has demonstrated to have good reliability, validity and precision.[9,24] It has been validated and used in context of Nepalese population.[25]

Diabetes is shown to increase the risk for periodontitis. Meanwhile, evidence also suggest that advanced periodontitis compromises glycemic control.[1,26] Exacerbated and dysregulated inflammatory responses are at the heart of the proposed two-way interaction between diabetes and periodontitis, and the hyperglycemic state results in various proinflammatory effects that impact on multiple body systems, including the periodontal tissues.[27] The diabetic patients predominantly suffer from psychological and psychosocial alterations that are due to local and systemic alterations. These local and systemic complications result in lowering of quality of life.[3] Meanwhile, periodontitis and its clinical consequences, such as tooth loss, have shown a considerable negative effect on OHRQoL, while periodontal treatment and alleviation of the symptoms can lead to improvement in OHRQoL. Tooth loss leads to functional deterioration in terms of chewing, which can have far-reaching consequences such as temporomandibular disorders and changes in an individual's diet and nutritional intake. It, therefore, impacts on the self-perceived aesthetics and social wellbeing. Moreover, social life, life experiences and self-confidence which are aspects of human nature deeply interwoven with perceptions of happiness are severely affected by the disease.[28]

It is noteworthy that the magnitude of severity as demonstrated in our study by CPI and LOA scores do not show significant difference in mean OHIP scores across all groups. This might hint towards lack of adequate precision of the QoL measure to identify difference among small groups as has been demonstrated in other studies.[29] Further studies using other OHRQoL measures are recommended. It should be emphasized that glycaemic control among diabetic patients may not be sufficient to address the quality of life of the patient unless underlying periodontal condition remains untreated. This calls for population specific programme with involvement of dental and medical professionals to minimize the effect of these comorbidities.

Conclusion
This study demonstrates the effect of periodontal disease in OHRQoL, as assessed by OHIP-14, among diabetic patients. Glycaemic control along with periodontal maintenance is required to enhance quality of life among such patients. This might be possible with comprehensive medical approach for diabetic patients. Hence, interventions should focus towards periodontal health of diabetics to ensure better quality of life.

Declaration
List of abbreviations
OHIP: Oral health Impact Profile
OHRQoL: Oral Health Related Quality of Life
CPI: Community Periodontal Index
LoA: Loss of Attachment
NA: Not Applicable

Ethics approval
The study was conducted after the ethical approval from Institutional Ethical Review Board (IERB), BPKIHS [Ref. Aca. 709/069/070]. Participants were explained about the research detail, its significance, the benefit and harm in Nepali language before obtaining the consent, their queries were answered. A statement indicating that the participants has understood all the information in the consent form and is willing to participate voluntarily was obtained. Participants were able to withdraw from

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the study at any time without giving any reason during the study period. The confidentiality of participants was assured and code number was used in each interview schedule and name of the participants was not mentioned anywhere.

Authors' information
TKB, AS, SKA, UG are faculties of Public Health Dentistry; JR is a faculty of Oral Medicine and Radiology; RM is a faculty of Internal Medicine.

Endnotes
aMann-Whitney U test, bKruskal-Wallis test; Bold signifies statistical significance at p<0.05 (Table 3)

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Jour of Diab and Endo Assoc of Nepal 2021; 5 (1): (3-9)
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Comparison of IDRS And ADA Diabetes Risk Assessment Tools Reveals Different Risk Score in Same Population: A Cross-Sectional Analysis in a Tertiary Care Hospital.

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Abstract

Background: To identify individuals at high risk of developing type2 diabetes (T2DM), use of a validated risk-assessment tool is currently recommended. Nevertheless, recent studies have shown that risk scores that are developed in the same country can lead to different results of an individual.The Objective of study was to reveal whether two different risk-assessment tools predict similar or dissimilar high-risk score in same population. **Method:** This cross-sectional analytical study was carried upon 336 non-diabetic adults visiting the outpatient department (OPD) of Medicine, MARKS Medical College & Hospital, Bangladesh from October 2018 to March 2019. Woman having previous history of Gestational Diabetes Mellitus (GDM) were also included. Both the Indian Diabetes risk Score (IDRS) and the American Diabetes (ADA) Risk Score questionnaire were used to collect the data on demographic and clinical characteristics, different risk factors of an individual subject, and to calculate predicted risk score for developing T2DM. **Results:** Among 336 subjects, 53.6% were female. The mean (±SD) age of the study subjects was 38.25±1.12 years. The average IDRS predicted risk score of developing T2DM was more in female subjects than male [p<0.05]. Whereas the ADA predicted increased risk score of developing type 2 diabetes was more in male subjects than female (p<0.05). IDRS categorized 37.2 % of individuals at high risk for developing diabetes; [p=0.10], while the ADA risk tool categorized 20.2% subjects in high risk group; [p<0.001]. **Conclusions:** The results indicate that risk for developing type 2 diabetes varies considerably according to the scoring system used. To adequately prevent T2DM, risk scoring systems must be validated for each population considered.

Keywords: Diabetes Risk Assessment Score, IDRS, ADA Diabetes Risk assessment Tools

Introduction

Diabetes mellitus (DM) is one of the most common non-communicable diseases (NCDs) globally. The prevalence and incidence of type 2 diabetes mellitus (T2DM) are increasing at fast speed in the world[1]. According to WHO (world health organization), the total number of people with diabetes is projected

to rise to 366 million in 20302, but International Diabetes Federation (IDF)[3] estimated that the situation is much worsened as the burden would increase from 417 million (2030) to 486 million (2045).

The prevalence of diabetes is increasing in Bangladesh in both urban and rural areas[4]. It increases healthcare use and expenditure and imposes a huge economic burden on the healthcare systems. Recent studies[5] have shown that lifestyle or medication intervention could prevent the

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incidence of type 2 diabetes. Hence, screening tools are needed to identify participants with undiagnosed diabetes or those who are at risk for developing diabetes in the future.

Studies[4] also support the utilization of risk-assessment scor¬ing systems in quantifying individual's risk for developing T2DM. For this purpose, numerous risk scores[6] recently have been proposed. Participants at high risk of developing type 2 diabetes, according to the risk score threshold, are thus amenable to preventive measures. Some scores have been validated in selected populations[7], prompting their use in other countries[8,9]. Nevertheless, recent studies[8] have shown that risk scores that are developed in the same country can lead to different results. Likewise, one equation validated in one country might not provide adequate estimates in another[9]. Moreover, the risk score has to be accurate enough to provide targeted warnings for the patients.

Finally, and to the best of our knowledge, no study has ever compared the results of differing these two scoring systems in Bangladesh. The current study aimed to compare the results of scores that estimate the risk of developing type 2 diabetes using risk assessment tools of Indian Diabetes Risk Score (IDRS) and The ADA (American Diabetes Association) risk score.

Methods

The cross sectional analytical study was conducted among randomly sampled 336 adult Bangladeshi male & female subjects. The study population consisted of non-diabetic adults visiting the outpatient department (OPD) of Medicine, MARKS Medical College & Hospital, a tertiary care hospital in Dhaka, Bangladesh from October 2018 to March 2019. Individuals with known type 1 or type 2 diabetes or any endocrine illness and with an apparent communicative, cognitive impair¬ment or physical disability were excluded from the study. Woman having previous history of Gestational Diabetes Mellitus (GDM) were also included.

With written informed consent, both the Indian Diabetes risk Score (IDRS) and the American Diabetes (ADA) Risk Score questionnaire were used to collect the data including demographic and clinical characteristics, different risk factors of an individual subject, and to calculate predicted risk score for developing T2DM within 10 years. We took permission of the institutional review board of the hospital for conducting the study.

Risk Assessment Scores

In Bangladesh, still we don't have any diabetes risk assessment scoring system of our own. After review of literature regarding risk factors of developing diabetes in Bangladesh, we also reviewed some other well validated risk assessment scoring systems for DM of different countries. We found the risk assessment tools of the Indian diabetes Risk Score (IDRS)[10] and American Diabetes Association (ADA),[11] to calculate diabetes risk score was more useful for the Bangladeshi adults.

The ADA developing type 2 diabetes risk tool was well developed and tested for validity and reliability on different population in different coun¬tries. Study showed that ADA scores performed well and robustly, while the ADA score performed somewhat better than other scoring system[12]. The IDRS has a sensitivity of 72.5% and specificity of 60.1% and is derived based on the largest population based study on diabetes in India[13].

Methods of calculation of Risk Score

Anthropometric measurements of height and weight were measured by a reliable height scale and weighing scale, respectively. BMI (Body Mass Index): weight in kilograms/square of height in meters (kg/m2) was categorized as underweight (≤18.5 kg/ m2), normal weight (BMI: <25 kg/m2), overweight (BMI: 25 – <30 kg/m2), obese (BMI: ≥30 -<40 kg/m2) and morbid obese (BMI: ≥40 kg/m2)[14]. Waist circumferences was measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest using a reliable measuring inch tape. Hypertension was

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defined as a systolic blood pressure ≥140 mmHg and/or dias¬tolic blood pressure ≥90 mmHg, or in case of use of anti-hypertensive medications was measured by a manual sphygmomanometer in standard conditions (measured 2 times after a 5-min rest between each measurement)[15].

All the participants were assessed for both IDRS and ADA risk score. IDRS needs answers for three questions and waist measurement. Whereas, ADA risk score needed to answer six questions and BMI measurement.

ADA Risk score:
The ADA risk score system[16] has seven risk factors correlating with the risk of developing T2DM and was used to detect a diabetes risk based on age, sex, BMI, physical activity, past history of gestational diabetes mellitus, family history, and history of hypertension. It demonstrates the probability of developing T2DM. If anyone score 5 or more; that person are at increased risk for having type 2diabetes.

IDRS system:
The IDRS system[17] has four risk factors correlating with the risk of developing T2DM and was used to detect a diabetes risk based on age, waist circumference, physical activity, family history of diabetes. Subjects with an IDRS of <30 was categorized as low risk, 30-50 as moderate risk and those with >60 as high risk for diabetes.

Data were analyzed with Statistical Package for Social Science (SPSS Inc, Chicago, Illinois, USA) software version 16. The means and standard deviations were used to describe continuous data. For categorical data, frequencies and percentages were estimated. Categorical variables were compared with each other using the chi-square test. P value <0.05 was considered as significant.

Results
Baseline characteristics
A total of 336 subjects were included. Among them, 46.4 % were male and 53.6 % were female. The mean (±SD) age of the study subjects was 38.25 ±1.12 years. Maximum age was 68 years and minimum was 22 years. Average (±SD) BMI (kg/m2) was 25.16 ± 3.57 and waist circumference (cm) was 85.38±8.37. The mean (±SD) blood pressure (mm Hg) of the study subjects were SBP: 114.70 ±11.40 and DBP: 75.11 ±8.91 (Table 1).

Table 1: Comparison of clinical-demographic features, IDRS & ADA risk score between male and female subjects (n=336)

Variables	Male (Mean ± SD)	Female (Mean ± SD)	Total (Mean ± SD)
Age (years)	38.47 ± 1.16	38.06 ± 1.10	38.25 ± 1.12
Height (meter)	1.65 ± 0.08	1.56 ± 0.06	1.60 ± 0.08
Weight (kg)	70.87 ± 1.17	61.07 ± 9.89	65.62 ± 1.18
WC (cm)	86.52 ± 8.22	84.99 ± 8.40	85.38 ± 8.37
BMI (kg/m2)	25.69 ± 3.73	24.70 ± 3.37	25.16 ± 3.57
SBP (mm Hg)	114.55 ±11.20	114.83 ± 11.60	114.70 ± 11.40
DBP (mm Hg)	74.55 ± 8.82	75.61 ± 8.97	75.11 ± 8.91
IDRS	45.44 ± 17.20	51.50 ± 19.64	48.69 ± 18.76
ADA Risk Score	3.63 ± 1.70	2.47 ± 1.76	3.01 ± 1.83

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WC: Waist Circumference; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; IDRS: Indian Diabetes Risk Score; ADA: American Diabetes Association

Risk assessment factors of IDRS

As stated in IDRS tool, most of the subjects (47.0%) were from < 35 years age group; [p=0.35]. According to waist circumference categories, female had high abdominal obesity in comparison to male (male vs. female: 4.5% vs.17.0%); [p<0.001]. Less than 50% of subjects do regular mild exercise or physical activities at home or work place (male vs. female: 18.8% vs. 24.7%); [p=0.14]. In the context of family history of diabetes, one diabetic parent had been found among 30.7 % of subjects and both diabetic parents had been found among 19.0% of subjects; [p=0.52] (Table-2).

Table 2. Prevalence of risk assessment factors for prediction of IDRS of developing type 2 diabetes among Bangladeshi subjects (n=336)

Risk Assessment Factors of IDRS			Male [N (%)]	Female [N (%)]	Total [N (%)]	p value
Age (years)		< 35 Years	76 (22.6)	82 (24.4)	158 (47.0)	0.351
		35-49 Years	47 (14.0)	67 (19.9)	114 (33.9)	
		≥ 50Years	33 (9.8)	31 (9.2)	64 (19.0)	
Waist Circumference (cm)	Male	Less than 90cm	73 (21.7)		73 (21.7)	<0.001
		≥ 90-99 cm	68 (20.2)		68 (20.2)	
		≥ 100 cm	15 (4.5)		15 (4.5)	
	Female	Less than 80 cm		54 (11.1)	54 (11.1)	<0.001
		80-89 cm		69 (20.5)	69 (20.5)	
		≥ 90cm		57 (17.0)	57 (17.0)	
Physical activity (30 min daily)		Regular Vigorous Exercise	1 (0.3)	0 (0.0)	1 (0.3)	0.147
		Regular Moderate Exercise	45 (13.4)	35 (10.4)	80 (23.8)	
		Regular Mild Exercise	63 (18.8)	83 (24.7)	146 (43.5)	
		No Exercise	47 (14.0)	62 (18.5)	109 (32.4)	
Family History of Diabetes		No Diabetes in Parents	81 (24.1)	88 (26.2)	169 (50.3)	0.585
		One Parent is Diabetic	49 (14.6)	54 (16.1)	103 (30.7)	
		Both Parents are Diabetic	26 (7.7)	38 (11.3)	64 (19.0)	

IDRS: Indian Diabetes Risk Score; Pearson chi-square test was done; P value <0.05 is significant.

Risk assessment factors of ADA

In accordance with ADA risk tool, most of the subjects (61.0%) were from <40 years age group; [p=0.28]. At best, 9.5 % of female subjects had previous history of GDM; [p<0.001]. More than 50% had a positive family history (mother, father, sister or brother) of DM (male vs. female: 25.0 % vs. 29.5 %); [p= 0.83]. A total 25.3% of the adults

Comparison of IDRS And ADA Diabetes Risk Assessment
Jour of Diab and Endo Assoc of Nepal 2021; 5 (1): (10-18)
ISSN Print 2594-3367   ISSN Online 2631-2107

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had past history of hypertension or were on anti-hypertensive medications; [p=0.37]. More than half of the adults (68.8 %) did not do daily physical activity; [p=0.44]. Some of the adults had high BMI [44.4 %were overweight and 11.0% were obese]; (p=0.11) (Table 3).

Table 3. Prevalence of risk assessment factors for ADA risk score of developing type 2 diabetes among Bangladeshi subjects (n=336).

Risk Assessment Factors for ADA Risk Score for Type 2 Diabetes		Male [N (%)]	Female [N (%)]	Total [N (%)]	p value
Age	< 40 Years	89 (26.5)	116 (34.5)	205 (61.0)	0.284
	40-49 Years	32 (9.5)	35 (10.4)	67 (19.9)	
	50-59 Years	22 (6.5)	22 (6.5)	44 (13.1)	
	≥ 60 Years	13 (3.9)	7 (2.1)	20 (6.0)	
History of GDM	Yes		32 (9.5)	32 (9.5)	<0.001
	No		148 (44.0)	148 (44.0)	
Family history of diabetes mellitus	Yes	84 (25.0)	99 (29.5)	183 (54.5)	0.832
	No	72 (21.4)	81 (24.1)	153(45.5)	
History of hypertension/ High Blood Pressure	Yes	43 (12.8)	42 (12.5)	85 (25.3)	0.374
	No	113 (33.6)	138 (41.1)	251(74.7)	
Daily Physical activity	Yes	52 (15.5)	53 (15.8)	105 (42.7)	0.443
	No	104 (31.0)	127 (37.8)	231(68.8)	
Weight Category; (BMI: kg/m^2)	Normal Weight (< 25 kg/m^2)	58 (17.3)	90 (26.8)	148 (44.0)	0.113
	Overweight (25 - <30 kg/m^2)	76 (22.6)	73 (21.7)	149 (44.3)	
	Obese (≥30 - <40 kg/m^2)	21 (6.2)	16 (4.8)	37 (11.0)	
	Morbid Obese (≥ 40 kg/m^2)	1(0.3)	1(0.3)	2(0.6)	

ADA: American Diabetes Association; BMI: body mass index; GDM: Gestational Diabetes Mellitus. Pearson chi-square test was done; p<0.05=significant.

Risk assessment score for type 2 diabetes among studied subjects
The mean IDRS predicted 10-year risk score of developing T2DM was more in female subjects than male; [p<0.05] (Table 1). According to IDRS system, 37.2 % of the subjects had high risk score for developing diabetes. Among them, 14.6% were male and 22.6 % were female. While 48.5% had moderate risk and 14.3% had low risk for developing diabetes; [p=0.10] (Figure 1).

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Figure 1: Different categories of IDRS assessment system among Bangladeshi subjects (n=336)
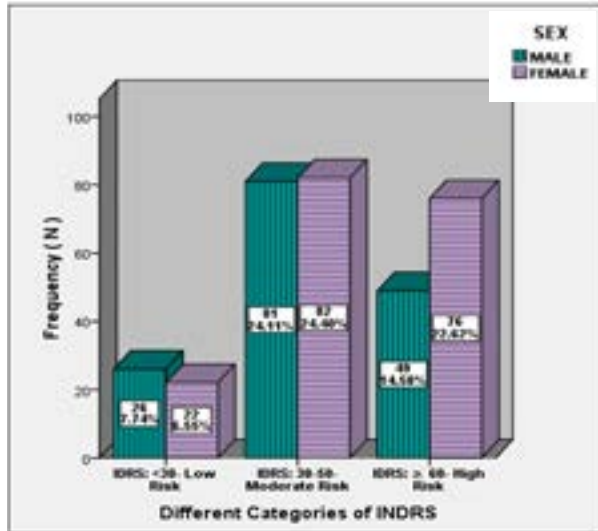
IDRS: Indian Diabetes Risk Score

IDRS predicts that 85.7% of the subjects may have moderate to high risk to develop T2DM within the consecutive 10 years, if no primary preventive measures are taken to curb it

The ADA predicted mean risk score of developing type 2 diabetes was more in male subjects than female; [p<0.001] (Table 1). A total 20.2 % of the subjects had high risk score (DRS ≥ 5) for developing dia¬betes. Among them, 13.4 % were male and 6.8 % were female; [p<0.001] (Figure 2).

Comparison between two risk scores
According to IDRS tools, 37.2% of the subjects were in high risk for developing diabetes (male vs. female: 14.8% vs. 22.6%); [p=0.10] (Figure 1). But the prediction of ADA risk tool for the same category was different. According to ADA risk tool, 20.2% of the subjects were in high risk group (male vs. female: 13.4 % vs. 6.8 %); [p<0.001] (Figure 2).

Figure 2: Different categories of ADA risk score among Bangladeshi subjects (n=336)
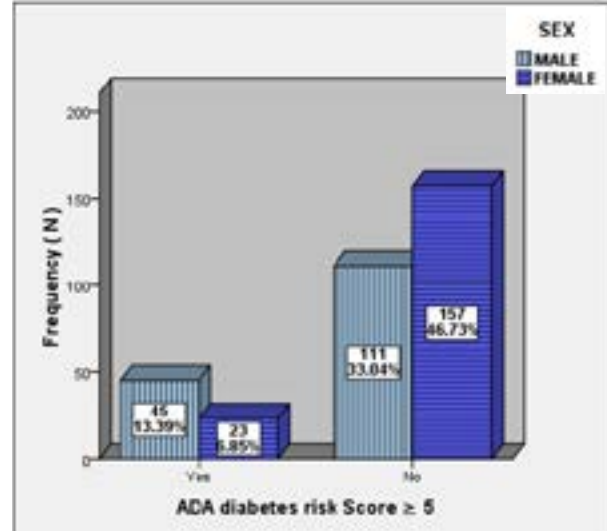
ADA: American Diabete Association

Discussion
The systematic review[18] shows that the predictive ability of diabetes risk scores, which have been developed in populations of varying ethnic backgrounds, differs considerably between populations. Several existing risk scores that enable prediction of type 2 diabetes based on information readily available in routine clinical practice or that can be gathered by questionnaires. Furthermore, these risk scores focus mainly on non modifiable risk factors such as age and family history or on the consequences of adverse health behaviors such as high body mass index and waist circumferences, high blood pressure, and medication use.

The feasibility of implementing any screening model will depend on the availability and completeness of the required risk factor data[19]. Risk scores show overall good discriminatory ability in populations for whom they were developed. However, discriminatory performance is more heterogeneous and generally weaker in external populations, which suggests that risk scores may need to be validated within the population in which they are intended to be used[19].

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The risk-scoring systems compared in this study shared several types of variables. For instance, both of them included family history, which can be explained by the association between certain genes and diabetes[20], and both of them also included age, which has been shown to be related to the risk of diabetes. Both scores also included obesity markers, such as BMI or waist circumference, all of which are involved in the metabolic syndrome definition[21]. Finally, these scores system included lifestyle habits (physical activity). For instance, age, obesity, and the other factors mentioned vary by country, and this may result in a differential importance to predict diabetes[22].

This study examined whether the adoption of two different validated risk-assessment tools would alter an individual's predicted risk of type2 diabetes. The risk assessments were chosen in this study primarily because they feature in the NICE guidance,[23] and also have some common risk variables that make comparisons feasible. Both the risk scores are based on noninvasive measurements that could be improved by adding commonly measured biochemical markers, in particular, measures of glycemia.

In agreement with previous studies[24,25] this study demonstrated that the risk of individual developing type2 diabetes was dependent on which risk-assessment tool was used. It was observed that the IDRS predicts that 37.2 % of the subjects may have high risk to develop T2DM within the consecutive 10 years. But the prediction of ADA risk tool was different for the same category. ADA risk assessment system predicts that 20.2 % of the subjects may have high risk to develop T2DM within the consecutive 10 years. Hence, diabetes risk scores demonstrated good discrimination in the study populations.

Conclusion

The adoption of a different valid risk assessment tool can alter the predicted risk of an individual and caution should be used to identify those individuals who really are at high risk of type 2 diabetes. To adequately prevent type2 diabetes, risk scoring systems must be validated for each population considered.

Limitation

This study is limited by the cross-sectional design and is not causal or effect study or measure of temporal changes. Validation of the risk assessment with a large sample size in different populations would have enhanced the generalizability of the results.

Future Research Proposal

This study reinforces the view that the main approach to managing this problem is to improve all stakeholders' understanding and compliance for development of national diabetes risk assessment tools and its widespread application campaigns. Unique diabetes risk assessment tools for Bangladeshi populations are needed. Population based study on risk factors that predicts future development of diabetes for our population should be carried out.

List of abbreviations

GDM : Gestational Diabetes Mellitus
OPD : Out Patient Department
IDRS : Indian Diabetes risk Score
ADA : American Diabetes Association Risk Score
SD : Standard Deviation
IDF : International Diabetes Federation
T2DM : Type 2 Diabetes Mellitus
WHO : world health organization
BMI : Body Mass Index
DRS : Diabetes risk score

Authors' contributions

Nazma Akter conceptualized, collected data, analyzed and wrote the manuscript. Nazmul Kabir Qureshi supervised and guided throughout the study from the beginning of the study and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Utility of hsCRP as an add on to Lipid Profile for Cardiovascular
Jour of Diab and Endo Assoc of Nepal 2021; 5 (1): (19-24)
ISSN Print 2594-3367   ISSN Online 2631-2107

ORIGINAL ARTICLE

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Utility of hsCRP as an add on to Lipid Profile for Cardiovascular Risk Stratification in Adults with Type 2 Diabetes Mellitus

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Abstract

Introduction: Dyslipidemia is common in Diabetes and is predictive of cardiovascular events. But, myocardial infarction in the setting of normal lipids levels is not uncommon. hsCRP has been studied elaborately and is found to be a stronger predictor of heart attack and stroke than LDL cholesterol. We conducted this study to observe the level of hsCRP in adults with Type 2 Diabetes and its association with lipid parameters. **Methods:** It is a cross sectional study including 168 Type 2 Diabetes patients conducted in department of biochemistry and internal medicine at B.P. Koirala Institute of Health Sciences, Dharan, Nepal for duration of one year. The ethical clearance was taken from the institutional ethical review board and patients were enrolled after taking informed consent. Venous blood was collected and serum lipid profile and hsCRP were measured. **Results:** The means±SD for age, TC, HDL-C, LDL-C and HDL/LDL ratio of patients were 52.2±11.9 years, 182.9±41.9 mg/dl, 41.6±8 mg/dl, 94.9±20 mg/dl, and 0.47±0.18 respectively. The medians of TG and hsCRP were 152.5 (109, 195) mg/dl and 1.9 (0.9, 2.8) mg/dl respectively. hs-CRP was found to have significant positive correlation with TC (r=0.286), LDL (r=0.652) and TG (r=0.299) and significant negative correlation with HDL (r= -0.614) and HDL/LDL ratio (r= -0.646). Only 33% of patients were categorised as having increased CVS risk according to high LDL levels but altogether 75% of patients had increased CVS risk according to hsCRP levels. **Conclusion:** hs-CRP can be considered as an add on to lipid profile while predicting CVS complications in patients with Type 2 Diabetes Mellitus in our population.

Keywords: Dslipidemia, hsCRP, Lipid Profile

Introduction

Pathogenesis of type 2 diabetes mellitus is much more complicated and involves many pathways leading to insulin resistance. A large body of data has recognized potential role of long standing inflammation in the causation Type 2 Diabetes[1,2]

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as well as in the progression of atherosclerosis and atherothrombosis.[3,4] High-sensitivity C-reactive protein (hsCRP) is an acute-phase response protein that is considered both a marker of inflammation and a predictor of cardiovascular events, including myocardial infarction,stroke, peripheral arterial disease, and sudden cardiac death.[5,6,7] Prospective studies have found high CRP levels to be predictive of the development of insulin resistance, the Insulin Resistance Syndrome and Type 2 diabetes.[8,9] Furthermore, cardiovascular morbidity and

Utility of hsCRP as an add on to Lipid Profile for Cardiovascular
Jour of Diab and Endo Assoc of Nepal 2021; 5 (1): (19-24)
ISSN Print 2594-3367   ISSN Online 2631-2107

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mortality is increased in patients with elevated CRP levels.[10] This adds to the evidence that chronic inflammation may be an underlying cause of both atherosclerosis and insulin resistance. hs-CRP has been widely studied and established as a marker which would reclassify patients into more accurate risk categories leading to more appropriate treatment decisions. Possibility of myocardial infarction occurring in setting of normal lipid levels is not uncommon. In an effort to better identify patients with high cardiovascular risk, several other biomarkers are being studied and hsCRP is one of the well studied ones. The recommendation suggests serum hs-CRP value below 1mg/l, 1-3 mg/l and >3mg/l to be associated with low, intermediate and high future cardiovascular risk.[11] Studies regarding this are scant in our population which made us to take up this study. We aimed to find the level of hs-CRP and its association with different parameters of lipid profile in our diabetic population. Unlike a prospective study, this cross sectional study would not be able to find causal relationships but will certainly lay down basis for further studies.

Materials and Methods

This study is a cross sectional study conducted in the department of biochemistry with collaboration of the department of internal medicine at B.P. Koirala Institute of Health Sciences, Dharan, Nepal for duration of one year. A total of 168 consecutive patients attending endocrinology OPD either diagnosed as Type 2 Diabetic as per American Diabetes Association guidelines or already taking treatment for Type 2 Diabetes have been enrolled in the study. Dyslipidemia has been defined as per the National Cholesterol Education Programme (NCEP) Adult Treatment Panel (ATP) III guidelines. The patients were included irrespective of duration of disease. Patients having severe anaemia, taking statins for dyslipidemia, having any metabolic instability, any type of cutaneous or systemic infection, any CVS or renal complications and not intending to take part in the study were excluded. The ethical clearance was taken from the institutional ethical review board and informed consent was taken from the participants. Blood samples were collected after a minimum of 8 hrs of fasting. 2 ml venous blood was collected into plain vial. Blood samples were allowed to clot and were centrifuged at 3000rpm for 5 minutes to separate the serum. Different parameters of lipid profile viz Total Cholesterol (TC), High density lipoprotein (HDL), Low density lipoprotein (LDL), Triglycerides (TG) and hsCRP were measured in serum. Analysis was done in fully automated closed system- Roche/Hitachi cobas c 311. Data were in entered in Microsoft Excel 2007 and analysed using SPSS.

Normally distributed data has been presented as mean and standard deviation and non parametric data as median and inter quartile range. Pearson correlation test has been used to find correlation between parametric data and spearman rho test for non parametric data. Comparison of means has been done by student's t test in parametric data with two groups. Comparison of median values has been done by Mann Whitney U test in non parametric data with two groups. P value less than 0.05 has been considered significant.

Results

This study is a cross-sectional study with an attempt to observe the role of hsCRP in stratifying CVS risk in Type 2 Diabetics. The correlation of inflammatory marker hsCRP has been found out with parameters of lipid profile viz. TC, HDL-C, LDL-C and TG. Out of 168 patients, there were 91 females and 77 males. They had different occupations, 30 of them were job holders in either government or private offices, 36 had their own business, 60 females were housewives, 14 were farmers and the rest 28 have been categorised into 'other' occupation. This includes occupations like daily waged labours, cobblers etc and those males who didn't work at all. Among 168 subjects, 20 were vegetarians and rest 148 consumed meat. Also, out of 168 subjects, 109 were hypertensive taking medications for the same, and rest 59 had normal blood pressure.

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The means±SD of age, TC, HDL-C, LDL-C and HDL/LDL ratio of patients were 52.2±11.9 years, 182.9±41.9 mg/dl, 41.6±8 mg/dl, 94.9±20 mg/dl, and 0.47±0.18 respectively. The medians of TG and hsCRP were 152.5 (109, 195) mg/dl and 1.9 (0.9, 2.8) mg/dl respectively. The differences in the levels of these parameters among male and female patients were calculated but were not found to be significant (Table 1).

Table 1 Biochemical parameters in males and females

	Male (77)	Female (91)	'p' value
AGE (years)	52.7±11.9	51.84±12.1	0.64a
TC (mg/dl)	176.3±42.4	188.4±41	0.06a
HDL (mg/dl)	40.9±9.2	42.1±6.9	0.32a
LDL (mg/dl)	95.1±19.8	94.7±20.3	0.9a
HDL/LDL	0.4±0.1	0.5±0.1	0.8a
TG (mg/dl)	130 (99, 179)	167 (124, 217)	0.05b
hs-CRP (mg/dl)	1.6 (1.0, 2.8)	2.0 (0.9, 2.7)	0.33b

a Independent t test   bMan whitney U test

Dyslipidemia has been classified according to NCEP ATP III guidelines and we found out that hypercholestrolemia, hypertriglyceridemia and increased LDL-C was seen in 36%, 50% and 33% of subjects respectively. Level of HDL-C was low in 47% of females and 16% of males. We divided patients into three and two different groups on the basis of hs-CRP level and LDL level respectively. hs-CRP level 1mg/L, 1-3mg/L and >3mg/L has been classified as low, average and high risk groups for CVS events by American Heart Association. LDL has been established as an independent marker for CVS events and has been suggested to be kept below 100mg/dl in Type 2 Diabetes Mellitus. Although only 33% of patients were categorised as having increased CVS risk according to high LDL levels, altogether 75% of patients had increased CVS risk according to hsCRP levels where 57% had moderate and 18% had high CVS risk. (Table 2).

Table 2 Distribution of LDL among three groups of hs-CRP

	hsCRP (mg/L)		
DL(mg/dl)	<1(n=42)	1-3(n=96)	>3(n=30)
<100	38	75	0
≥100	4	21	30

Shows distribution of LDL among three groups of hsCRP. hs-CRP was found to have significant positive correlation with TC (r=0.286, <0.01), LDL (r=0.652, <0.01) and TG (r=0.299, <0.01) and significant negative correlation with HDL (r= -0.614, <0.01) and HDL/LDL ratio (r= -0.646, <0.01). It was found that values of TC, LDL, and TG were significantly higher in patients having >3mg/L of hs-CRP than those having hs-CRP 1-3 mg/L, which was in turn higher than those having hs-CRP <1mg/L. Also the levels of HDL and HDL/LDL ratio was significantly lowest in subjects having >3mg/L hs-CRP and highest in subjects having hs-CRP <1mg/L. (Table 3) elaborates values of parameters of lipid profile among 3 groups according to hsCRP.

Table 3 Comparison of different parameters of lipid profile among three groups of hs-CRP.

hs-CRP \ (mg/L)	<1	1-3	>3	'p' value
TCa (mg/dl)	154±35	191±39	196±41	<0.01*
HDLa (mg/dl)	47±7	43±6	33±5	<0.01*
LDLa (mg/dl)	83±12	92±20	114±14	<0.01*
HDL/LDLa	0.6±0.2	0.5±0.2	0.3±0.1	<0.01*
Triglyceridsb (mg/dl)	105 (99,158)	158 (121,127)	195 (135,263)	<0.01*

aANNOVA, bKruskal-Wallis test. * Significant at the level of p=0.01.

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Jour of Diab and Endo Assoc of Nepal 2021; 5 (1): (19-24)
ISSN Print 2594-3367   ISSN Online 2631-2107

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Discussion

Dyslipidemia is a well-recognized CVS risk factor among diabetics. The typical diabetic dyslipidemia consists of high total cholesterol, triglycerides, LDL-C and low HDL-C. Among these, the LDL-C has been considered to be most atherogenic and hence requires strict control. But, Although LDL cholesterol still remains a highly contributary risk factor for cardiovascular disease, at least one-third of coronary events occur in individuals with LDL levels < 130 mg/dl, which is generally considered an average level in individuals without overt coronary artery disease.[12] One study[13] even quoted "Half of all myocardial infarctions occur in persons in whom plasma lipid levels are normal". This caused the scientific world to look into several other markers which would be able to improve detection of subclinical atherosclerosis. Some of such markers are lipid parameters like lipoprotein (a), apolipoprotein (apo) A-ı and Apo B-100; inflammatory biomarkers like C reactive protein and fibrinogen and nutritional biomarkers like total plasma homocysteine.

A prospective study compared CVS risk predicting capabilities of[12] such markers and concluded that hsCRP level was most powerful predictor in univariate analysis.[14] Our study showed that among the lipid parameters, the commonest one to be raised was serum Triglyceride level followed by Total cholesterol and then LDL levels suggesting hypertriglyceridemia to be the commonest lipid abnormality in the diabetics of our population as well. Females showed higher value of TG than males. The median hsCRP value was 1.9 mg/L, which indicates moderate CVS risk. Females had higher hsCRP level than males. This finding is in accordance with a study done by Graziella et al15 involving 3249 Type 2 Diabetic patients. They also found out that with respect to people with CRP values in the lowest tertile (<1.6 mg/L), those with CRP values in the highest tertile (> 4.4mg/L) had significantly higher values of TC, LDL, TG and significantly lower values of HDL. These finding match exactly with the results seen in our study and the differences are statistically highly significant.

Our study shows significant positive correlation between hs-CRP and parameters of lipid profile and significant negative correlation between hs-CRP and HDL. These findings are exactly in agreement with findings of a comparative study done by Palvasha et al.[16] They have found the similar correlations of hs-CRP and ferritin (marker of inflammation) with parameters of lipid profile. Similar findings are shown by studies done by Sung et al.[17] and Rhee at al.[18] CRP is a strong predictor for CVS events and according to Ridker et al, it is stronger predictor of heart attack and stroke than LDL cholesterol.[19] A study was aimed to find out relationships between the LDL cholesterol and CRP levels achieved after treatment with statins and the risk of recurrent myocardial infarction or death from coronary causes among 3745 patients with acute coronary syndromes. They found out that patients who had low CRP levels after statin therapy had better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL cholesterol and hence suggested that strategies to lower cardiovascular risk with statins should include monitoring both CRP as well as cholesterol.[20] LDL has been established as an independent marker of CVS risk and its serum level has been suggested to be kept below 100mg/dl in Type 2 Diabetes. In our study there were 75 patients, who had normal level of LDL, <100mg/dl but hs-CRP was in the range of moderate CVS risk, i.e. 1-3mg/L (Table 2). It would be beneficial to be more cautious with these kinds of patients and start the recommended interventions to reduce CVS risk.

Low-grade inflammation plays an important role not only in the pathogenesis of Diabetes mellitus but also has an association with dyslipidemia in the diabetics. Elevated CRP levels have been associated with obesity, dyslipidaemia and hypertension, and are found in insulin-resistant patients with Type 2 diabetes.[21, 22] Many evidences support the causal role of CRP in CVS diseases. There is convincing experimental evidence linking C-reactive protein to plaque disruption and the onset of cardiovascular events. C-reactive protein mRNA and protein has been found to be abundantly present in

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atherosclerotic lesions.[23] The interventions known to reduce CVS risk e.g diet, exercise, cessation of smoking, and controlling blood pressure, also decrease hs-CRP levels.[24] CRP has been found to be stronger predictor of heart attack and stroke than LDL and also persons having high CRP and Low LDL have a higher CVS risk than those having low CRP and high LDL.[19] With all these knowledge in mind, if we measure levels of hs-CRP routinely in the patients of Diabetes, we will be able predict and delay CVS complications especially in those patients who have normal level of LDL and are considered to have low CVS risk.

Conclusion

Though estimation of hs-CRP is not performed routinely in patients of Type 2 Diabetes, all these studies and results from our study encourage to evaluate its level alongside lipid profile so that we can predict CVS complications earlier and better, and intervene accordingly to prevent them.

List of abbreviations

1. hsCRP : High sensitivity C reactive protein.
2. NCEP ATP III : National Cholesterol Education Programme Adult Treatment Panel.
3. CVS : Cardiovascular system.
4. TC : Total cholesterol.
5. HDL : High density lipoprotein.
6. LDL : Low density lipoprotein.
7. TG : Triglycerides.

Ethics approval and consent to participate

This study is a cross sectional study conducted in the department of biochemistry with collaboration of the department of internal medicine at B.P. Koirala Institute of Health Sciences, Dharan, Nepal for duration of one year. The ethical clearance was taken from the institutional ethical review board and informed consent was taken from the participants prior to conducting the study.

Consent for publication

Not applicable

Competing interests

None

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Journal of Diabetes and Endocrinology
Association of Nepal

Perceived self-efficacy and self-care practices among diabetic patients in a Tertiary Hospital, Nepal

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Abstract

Background: Diabetes Mellitus (DM) is a major public health problem worldwide and Nepal is not an exception. Complications of DM are in rise which results in major disabilities and poor quality of life. But evidences show that adoption of self-care practices can prevent those complications leading a healthy and quality life. Self-care practice is closely related to self-efficacy. Thus, present study aimed to assess perceived self-efficacy and self-care practices and to examine relationship between perceived self-efficacy and self-care practice of patients with Diabetes. **Methods:** This analytical cross-sectional study conducted in Patan Hospital among 100 patients was reviewed and approved by Institutional Review Committee. Samples were selected purposively and data was collected by face to face interview technique. Diabetes Self-Efficacy Scale and self-care practice questionnaire was used to measure self-efficacy and self-care practice, respectively. **Results:** Fifty nine percent and 81% of participants had moderate level of perceived self-efficacy and good self-care practice, respectively. There was significant moderate positive (r=0.62, p<0.001) correlation between perceived self-efficacy and self-care practice even after controlling the variables (e.g. age, gender and participation in educational program regarding self-care). **Conclusion:** The self-efficacy of participants was moderate and self-care practice was good. However, self-care practice was very low on foot care and exercise. The significant positive relationship between perceived self-efficacy and self-care practice highlights the need for conducting educational activities for patients with DM to increase self-efficacy thereby increasing self-care practice.

Keywords: Diabetic patients, Perceived self-efficacy, Self-care practices.

Background

Diabetes Mellitus (DM) is a major public health problem worldwide.[1] Globally, the number of adults living with DM was 463 million in 2019, of which, 79% were living in low and middle income countries.[2] The global prevalence of DM is estimated to increase from 8.8% in 2015 to 10% in 2030.[3] On the other hand, the burden of diabetes has been increased at a greater rate in low and middle-income countries than in high income countries, both in terms of prevalence and number of adults

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with DM.[4] Nepal is not an exception where, it has been estimated that the prevalence of DM will increase from 4.5% in 2013 to 5.4% in 2035.[5] There were 696,900 cases of DM in Nepal in 2019 which is 4% of the total adult population (17,570,100).[2] The systematic review and meta-analysis from 2000 to 2014 showed that the prevalence of type 2 DM in Nepal was 8.4%, of which 8.1% in urban population and 1.0% in rural population.[6] Similarly, the global DM attributed mortality has been increased by 34.7% which is higher to Type 2 DM.[7] In Nepal, the mortality related to DM has increased from 2% to 4% from 2010 to 2016.[8,9]
The common diabetes related complications found in Nepalese people are retinopathy (37.3%), diabetic foot (30.4%), peripheral neuropathy (7.8%),

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Jour of Diab and Endo Assoc of Nepal 2021; 5 (1): (25-32)
ISSN Print 2594-3367   ISSN Online 2631-2107

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cardiovascular diseases (2.9%), and nephropathy (2%)[10], leading to major disabilities that require majority of resources to be used to treat diabetes complications.[11,12] However, people with diabetes can live long and healthy lives if their diabetes is early detected and well-managed.1 In order to reduce this burden, there are various modifiable risk factors which can be modified through behavioral changes and patients with diabetes need to adopt self-care behaviors to improve both the quality of life and life expectancy.[1,11] On the basis of sustainable development goal 3, Nepal has targeted to reduce death from diabetes out of all deaths from 1.7% to 0.5% from 2014 to 203013 which can be achieved by preventing the complications of DM.

Patient's perceived self-efficacy has been shown to have positive correlation with self-care practice.[14] It refers to the level of self-confidence of a person in performing particular goal-directed behavior successfully.[15] In context of DM, these goal-directed behaviors, refer to the self-care practice that patient with DM needs to follow on a daily basis including dietary control, physical activity, adherence to medication, foot care and monitoring blood glucose level[16] which helps to reduce the complications or delay the complications thereby increase the quality of life of patients with DM. A self-efficacy education program on foot self-care behavior of patients with diabetes showed that after the intervention, self-efficacy increased significantly from baseline (median = 30.00 to 44.00, Z = -4.76, p<0.001) and also self-care behavior levels significantly increased from baseline (median = 45.00 to 69.00, Z = -4.86, p<0.001).17 Another study showed that higher the self-efficacy score was significantly associated with active self-management behaviors (odds ratio = 1.06; 95% CI: 1.04 – 1.08).18 Thus, it can be concluded that self-efficacy and self-care behavior of patient with diabetes might have a causal relationship.

The level of self-care practices of patients with DM vary among different countries and also among different regions within the country as well.

In Nepal, there are studies carried out to assess the self-care practice of patients with DM. For instance, it was found that 61.8% of the patients had good practice in a study conducted in Eastern region (Dharan)[19] whereas, it was 47.3% in a study conducted in Western region (Pokhara).[20] Similarly, in regard of self-efficacy, it was found moderate and its relationship to self-care practice was positive (r=0.47, p<0.001).[14] In conclusion, self-care practices of patients with DM are different within country and self-efficacy of Nepalese patients with DM has not been explored much. Self-care practices are the activities which are economical and can be carried out by patients themselves to prevent the complications of DM.

The differences found in the results of various studies carried out within the country might have been due to different level of perceived self-efficacy of the patients in various places as it has shown strong correlation with the self-care practices. There are very few studies that explored the perceived self-efficacy and its relationship with self-care practices of the patients with DM in Nepal, thus it is very important to assess the perceived self-efficacy and self-care practices among the patients with DM and their relationship so that interventions can be applied to build up the confidence of the patients in carrying out the self-care activities thereby reducing the complications of DM. Hence, the present research aimed to determine the level of perceived self-efficacy, self-care practices among patients with diabetes and their relationship. This study was guided by Nola J. Pender's health promotion model (1996)[15] where individual characteristics and experiences may directly affect the self-efficacy and self-care practices of patients and the self-care practices may differ with the level of perceived self-efficacy of the patients.

Methods

A cross-sectional analytical study was carried out at Medical Outpatient Department (OPD) of Patan Hospital, Kathmandu, Nepal between September and November 2019.

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All patients with Type 2 Diabetes Mellitus (T2DM) who were receiving care at Patan Hospital were the study population. We purposively selected 100 samples from patients with T2DM aged ≥ 18 years old who have been diagnosed with T2DM for at least 1 year duration and willing to participate in the study. Patients with Type 1 DM, gestational diabetes were excluded from the study and, also patients with Type 2 DM who were not able to perform activities by themselves and did not understand Nepali language were excluded from the study.

The study was conducted after the ethical approval from Institutional Review Committee, Patan Academy of Health Sciences (Ref: PNC 1906141255). Participants were explained about the research detail, its significance, the benefit and harm in Nepali language before obtaining the consent, their queries were answered. A statement indicating that the participants has understood all the information in the consent form and is willing to participate voluntarily was obtained. Participants were able to withdraw from the study at any time without giving any reason during the study period. The confidentiality of participants was assured and code number was used in each interview schedule and name of the participants was not mentioned anywhere.

Data were collected using Diabetes Self-Efficacy Scale (DSES)[21] for perceived self-efficacy and self-developed self-care practice related rating scale for self-care practices. Initially self-care practice questionnaire was developed in English. Both tools were forward and backward translated utilizing the guideline [22,23] The content validity was done (CVI = 0.96). The Cronbach's alpha of the original DSES tool was 0.85.[24]

Self-efficacy: Diabetes Self-Efficacy Scale (DSES) was used to measure perceived self-efficacy. It is an 8 item 10-point rating scale developed by Self-Management Resource Center. It was modified into a 5-point rating scale as of previous literature considering the cultural context of Nepal where

1 is not at all confident and 5 is totally confident. The Cronbach's alpha of the modified tool in the previous study was 0.78.[24] The total score ranges from 8 to 40. Mean of 8 items is the score for the scale. Higher score indicates higher self-efficacy. Level of perceived self-efficacy was categorized into three levels: High (≥4), Moderate (3 – 3.9) and Low (<3).[25]

Self-care practice: Self-developed questionnaire for self-care practice was used to measure self-care practice. It is a 5-point rating scale in which 5 indicates always, 4 indicates often, 3 indicates sometimes, 2 indicates rarely and 1 indicates never. It consisted of 24 items with 5 domains namely; Diet, Medication, Exercise, Foot care and Blood Glucose Monitoring. Total score ranges from 24 to 120. Mean of the total scores of 24 items was the overall score for the scale. The level of self-care practices was categorized into two levels based on interquartile range where good self-care practice is score >3 and Poor self-care practice is score ≤3.[26] Informed written consent in Nepali language was obtained from each participant. Data was collected by face to face interview using semi-structured interview schedule in Nepali language at OPD setting before doctor check-up. It took approximately 35 minutes for each participant. Each day, 2 to 6 participants were interviewed according to the availability of the participants for a month. Statistical Package for Social Sciences version 16 was used for analysis of data. Descriptive statistics and Pearson's Correlation Coefficient was used for analysis. Data were checked for normal distribution using both graphical presentation (Q-Q plot and histogram) and statistics (Kurtosis, Skewness and Saphiro-Wilk test). It was found that the data were normally distributed. Level of significance was set at 0.05 level.

Results

The median age of participants was 55 years (IQR=15) and most of the participants were female middle aged and most of them had not participated in any self-care practice of DM related educational program (Table 1).

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ISSN Print 2594-3367   ISSN Online 2631-2107

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Table 1. Demographic Characteristics of Patients with Diabetes

N = 100

Variables	Frequency	Percentage
Age (in years)		
20 – 39	2	2
40 – 64	73	73
≥ 65	25	25
Median Age ± IQR = 55 ± 15		
Gender		
Male	31	31
Female	69	69
Attended educational program regarding self-care practice of DM		
Yes	17	17
No	83	83

IQR: Interquartile Range

Self-efficacy and self-care practice
Most of the participants (94%) had moderate to high level of self-efficacy. However, based on the mean score the self-efficacy was moderate (Table 2). Regarding self-care practice, 81% of participants had good self-care practice and based on the mean score the average self-care practice was good (Table 2).

Table 2. Level of Perceived Self-efficacy and Self-care Practice of Patients with Diabetes N = 100

Level of perceived self-efficacy	Frequency	Percentage
High perceived self-efficacy (score ≥4)	35	35
Moderate perceived self-efficacy (score 3 – 3.9)	59	59
Low perceived self-efficacy (score <3)	6	6
Mean ± SD = 3.73±0.56		
Level of self-care practices		
Good self-care practice (score >3)	81	81
Poor self-care practice (score ≤3)	19	19
Mean ± SD = 3.35 ± 0.40		

SD: Standard Deviation

When analyzing each domain of self-care practice, the highest self-care practice carried out by the participants was on blood glucose monitoring, followed by medication, diet, and lowest was on foot care and exercise (Table 3).

Table 3. Mean score and standard deviation of each domain of Self-care Practice N = 100

Domains	Total number of items in the domain	Minimum score	Maximum score	Mean	SD
Diet	8	2.38	4.75	3.88	0.44
Medication	4	2.75	5.00	4.01	0.60
Exercise	2	1.00	5.00	2.39	0.96
Foot Care	7	1.00	5.00	2.23	0.76
Blood Glucose Monitoring	3	2.67	5.00	4.35	0.63

SD: Standard Deviation

Correlation between self-efficacy and self-care practice
There was significant positive moderate correlation (r = 0.62, p < 0.001) between perceived self-efficacy and self-care practice of participants even after controlling age, gender and education regarding self-care practice (Table 4).

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ISSN Print 2594-3367   ISSN Online 2631-2107

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Table 4. Correlation between Perceived Self-efficacy and Self-care Practices of Patients with Diabetes N = 100

Control variables	Zero-order correlation		
		Perceived Self-efficacy	Self-care Practice
None	Perceived Self-efficacy	1	
	Self-care Practice	0.63*	1
Control variables	Partial correlation		
		Perceived self-efficacy	Self-care practice
Age, gender and attending educational program	Perceived self-efficacy	1	
	Self-care practice	0.62*	1

*. Correlation is significant at the 0.01 level (2-tailed).

Discussion

The average perceived self-efficacy of the participants was moderate. This finding is similar to the study conducted in Indonesia.[25] However, in a study conducted in Malaysia average perceived self-efficacy among patients with diabetes was high.[16] The individual characteristics and experiences of participants may directly affect their perceived self-efficacy.[15] In this study, personal factors (age, gender, and attending educational program related to diabetic self-care practices) may have affected the perceived self-efficacy of participants but its effect has not been studied in this study. These factors may have direct effect on the self-efficacy of participants as suggested by the Health Promotion Model which implies, younger patients may have higher self-efficacy than elder patients and patients who have attended educational programs may have better self-efficacy. Some of the factors as explored by previous studies that affect perceived self-efficacy are educational level, diabetes distress, and depression.[27] Self-efficacy is found to be higher among patients having higher educational level and lower among depressed and distressed patients.[27]

Regarding self-care practice, average self-care practice of participants was good. This finding is similar to the study conducted in Dharan, Nepal19 and also a study conducted in Ethiopia.[28] On the other hand, in a study conducted in India[29] and in Pokhara, Nepal[20], the average self-care practice of participants was poor. The self-care practices of the patients with diabetes at different places of

Nepal are found to be different. It may be due to various factors such as characteristics of patients or their level of self-efficacy as suggested by the Health Promotion Model of Pender. The clients who never attended diabetes health education program had 4 times more chances of having poor self-care practice (AOR = 4.09, 95% CI 1.89,8.84, p <0.001) than who had attended the program.[28] On the other hand, it was found that males, who had higher education, and those with a higher per-capita income were found to have better self-care practices in most aspects like physical exercise, regular blood sugar testing and follow up visits.[29] However, in this study, when analyzing the score the average score falls on the lower boarder (i.e. 3.35) indicating that there is still need to increase the level of self-care practice of patients with DM. It is important to conduct similar studies at various parts of the country to generalize the actual scenario of the self-care practices of patients as a whole. In this study, about 20% of participants had poor self-care practice, who are at higher risk of developing diabetes related complications which will affect their quality of life and also increase the health care expenditure.

When analyzing the domain of the self-care practice, the highest self-care practices carried out was on blood glucose monitoring followed by medication whereas, least performed self-care practice was on foot care. This finding is similar to the study conducted in India.[30] However, in the

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study conducted in Malaysia[16], least performed self-care was blood glucose testing. The findings of this study suggest that it is necessary to focus on the least performed self-care practice of participants which is on foot care and exercise as it has been found that about 30% of diabetic related complications in Nepali patients with DM are diabetic foot.[10] There are various factors which affect the self-care practices of patients with DM such as education level, employment status, and duration of illness, perceived social support, and perceived self-efficacy[19] as demonstrated by various studies suggesting exploring the factors affecting the self-efficacy of patients with DM in different settings.

In this study, there was significant moderate positive correlation between perceived self-efficacy and self-care practice of participants (r = 0.62, p-value < 0.001) even after controlling the variables such as age, gender and attending educational program. This finding is similar to the study conducted in Malaysia (r = 0.538, p < 0.001)19 and Iran (r = 0.39, p < 0.001).[31] This positive relationship between self-efficacy and self-care practice implies that one of the measures for improving self-care practices of the patients with DM is to uplift their self-confidence in performing those activities. Improving their self-care practices will help to prevent the complications of diabetes.

Limitation of the study
The findings of the study may not be generalized to all the patients of DM in Nepal as it was conducted in only one setting at tertiary hospital. Probability sampling technique covering the larger population may help to generalize the study findings.

Conclusion
The average self-efficacy of patients with DM was moderate and self-care practice was good. However, the score of good self-care practice was on lower side indicating that there is still a need to increase the level of self-care practice of patients with DM. The higher self-efficacy was associated with good self-care practice suggesting that there is a need to

increase the level of self-efficacy of patients with DM from moderate to high self-efficacy.

Declarations
List of abbreviations
CVI: Content Validity Index
DM: Diabetes Mellitus
DSES: Diabetes Self-Efficacy Scale
OPD: Out Patient Department
SD: Standard Deviation
T2DM: Type 2 Diabetes Mellitus

Consent for publication
Not applicable
Competing interests
The authors declare that they have no competing interests.
Funding
Not applicable

Authors' contributions
ND conceptualized, collected data, analyzed and wrote the manuscript. BP supervised and guided throughout the study from the beginning of the study and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Jour of Diab and Endo Assoc of Nepal 2021; 5 (1): (25-32)
ISSN Print 2594-3367   ISSN Online 2631-2107

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Adequacy of Thyroid Hormone Replacement in a Tertiary Care Hospital in Nepal-An Observational Study

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Abstract

Background: The therapeutic goal in hypothyroidism is to achieve patients' well-being and restore serum thyrotropin (TSH) to levels within the reference range. However, inadequate or over replacement is common in patients receiving levothyroxine. The Objective is to assess the treatment outcome of hypothyroid patients visiting outpatient clinic of medicine department of Kathmandu University Hospital, Dhulikhel, Nepal. **Method:** This is a cross sectional study on diagnosed Primary Hypothyroid patients who were taking levothyroxine replacement for at least six months. Patients were defined as euthyoid if their TSH was in the normal range (0.3-3.6 mmol/L) according to the hospital laboratory. Similarly patients were defined as over treated if TSH is <0.3 mmol/L and undertreated if TSH is >3.6 mmol/L. **Results:** A total number of 126 patients were enrolled for this study where mean age of participants was 40.88 ± 11.47 years and only 15 (11.1%) were male. Mean duration of hypothyroidism was 3.45 ± 2.57 years and mean Levothyroxine dose was 58.93 ± 26.89 mcg. In this study, nearly 70% of participants have normal TSH level. Similarly, 21% of participants have higher level of TSH and 9% have low TSH level. Multivariate logistic regression analysis did not show any significant co relation between treatment outcome and various variables. **Conclusion:** Treatment of hypothyroidism with levothyroxine being most effective, easily available, simple regimen and not costly, still one third of patients are not meeting the treatment outcome. However, being the pioneer study from Nepal, this study suggests improved treatment outcomes compared to similar studies from other countries.

Keywords: Primary Hypothyroidism, Treatment Outcome, Levothyroxine

Introduction

Diseases of the thyroid gland are amongst the most abundant endocrine disorder in the world second only to diabetes mellitus.[1] The spectrum of thyroid disorders includes hypothyroidism, subclinical hypothyroidism, hyperthyroidism and subclinical hyperthyroidism. The worldwide prevalence of spontaneous overt hypothyroidism is between 1% and 2% and ten times more common in women than in men.[2] The prevalence of overt hypothyroidism has been reported between 3.5% and 4.2% in various studies across India.[3,4] Several studies in different parts of Nepal showed wide variation in prevalence of the thyroid dysfunctions.[5, 6, 7]

Thyroid hormone replacement with synthetic levothyroxine is the treatment of choice for hypothyroidism, commonest thyroid disorder.[3-7] The therapeutic goal in hypothyroidism is to achieve

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patients' well-being and restore serum thyrotropin (TSH) to levels within the reference range.[8]

However, inadequate or over replacement is common in patients receiving levothyroxine.[9,10] Abnormal thyroid function tests were also detected in a third of patients who self-reported thyroid disease or use of thyroid medications in the National Health and Nutritional Examinations Survey (NHANES III).[11] Likewise, a study in older levothyroxine users showed that only 43% were biochemically euthyroid.[12] Unfortunately, to the best of our knowledge, we do not have outcome study on diagnosed hypothyroid patients from Nepal. Thus, this study aim to assess the treatment outcome of hypothyroid patients visiting outpatient clinic of medicine department of Kathmandu University Hospital, Dhulikhel, Nepal.

Methods

This is a cross sectional study on diagnosed Primary Hypothyroid patients attending the Medicine OPD of Dhulikhel Hospital, Kathmandu University Hospital from November 2017 to April 2018. People aged 18 years or above and who are taking Levothyroxine for at least 6 months were included in this study. Once patients visit the outpatient clinic of medicine, their socio-demographic data including duration of hypothyroidism, recent TSH level, medicine they are taking, current dose and lab investigations are documented in one demography form after written consent. Patients were defined as euthyoid if their TSH was in the normal range (0.3-3.6 mmol/L) according to the hospital laboratory. Similarly patients were defined as over treated if TSH is <0.3 mmol/L and undertreated if TSH is >3.6 mmol/L. Adherence to Thyroxine therapy was assessed by asking the patients the number of doses missed in the last 1 month and was categorized as non-adherent if misses >15% of doses in last month.[13] Data was analyzed using SPSS version 21.0 for windows. Descriptive statistics, such as frequency, percentage, mean and standard deviation was used to summarize patients' baseline characteristics. Multivariable logistic regression model was fitted to determine independent predictors of treatment outcome when the p-value ≤ 0.1 on bivariate analysis. Statistical significance was considered at p-value < 0.05. This study was approved by KUSMS-IRC.

Results

A total number of 126 patients were enrolled for this study whose characteristics variables are shown on Table 1. The mean age of participants was 40.88 ± 11.47 years, where only 15 (11.1%) were male. Majority of them (62%) have education level below SLC. Mean duration of hypothyroidism was 3.45 ± 2.57 years and mean Levothyroxine dose was 58.93 ± 26.89 mcg. All of the participants were neither smoker nor alcoholic. Likewise, none of the participants were non adherent in this study.

Forty percentage of participants were on Levothyroxine 50 mcg. Likewise, 23% of participants were on Levothyroxine 25 and 50 mcg each as shown on (figure 1).

In this study, nearly 70% of participants have normal TSH level. Similarly, 21% of participants have higher level of TSH and 9% have low TSH level as shown in (figure 2). Multivariate logistic regression analysis did not show any significant co relation between treatment outcome and age, gender, education level, disease duration, other comorbid conditions.

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Table 1: Characteristics of participants

Variables	Mean ± SD / Number (%)
Age (years)	40.88 ± 11.47
Gender	
Male	15 (11.1%)
Female	111 (88.1%)
Education	
Below SLC	78 (61.9%)
Intermediate	21 (16.66%)
Bachelor & above	27 (21.44%)
Duration of Hypothyroidism (years)	3.45 ± 2.57
TSH level (current)	3.36 ± 2.84
Free T4 level (mmol/L)	1.05 ± 0.24
Daily Levothyroxine Dose (Mcg)	58.93 ± 26.89
Weight (Kg)	63.83 ± 15.07
Blood Pressure	
SBP (mmHg)	81.61 ± 15.78
DBP (mmHg)	81.61 ± 15.78
Total Cholesterol (mmol/L)	171.83 ± 68.89
HDL (mmol/L)	43.01 ± 19.37
LDL (mmol/L)	98.66 ± 42.54
TG (mmol/L)	145 ± 72.07
Diabetes Mellitus	9 (7.12%)
Hypertension	9 (7.12%)
Dyslipidemia	9 (7.12%)

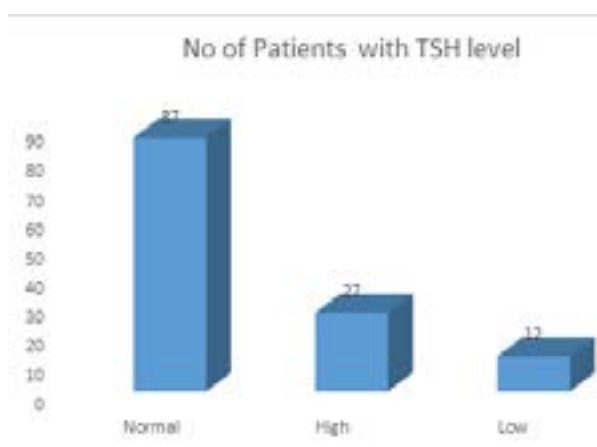*Figure 1: Proportion of patients taking daily Levothyroxine dose*

Figure 2: Number of patients based on TSH level

Discussion

In this study, almost 70% of participants have achieved euthyroid status, similar to the National Health and Nutritional Examinations Survey[14] and a general population study[15] published on 2011. Several other studies have shown that less than half of hypothyroid patients achieved euthyroid status despite of regular dose titration and follow up[13,16,17]. The proportion of undertreated hypothyroid patients was 21% in our study[15], which was 17% and much higher to other studies up to 45%[13,16,17]. Nearly 20% of participants had over replacement in one study[15], in contrast which was only 9% in this study, similar to the other studies[13,17]. Whatever the percentage, there is similar trend on treatment outcome between various studies that overtreatment being the least prevalent.

Both under and over replacement with levothyroxine could lead to potential unwanted consequences. Hypothyroidism is associated with harmful effects on body weight[18], lipid profile[19], blood pressure[20], and increased risk of sleep apnea[21].

The mean daily dose of levothyroxine in this study was 0.92 mcg/Kg. This dose is much lower to the daily recommended dose of 1.6 mcg/Kg by various western guidelines such as the American Thyroid Association and American Association of Clinical Endocrinologists guidelines[22]. There is one Asian
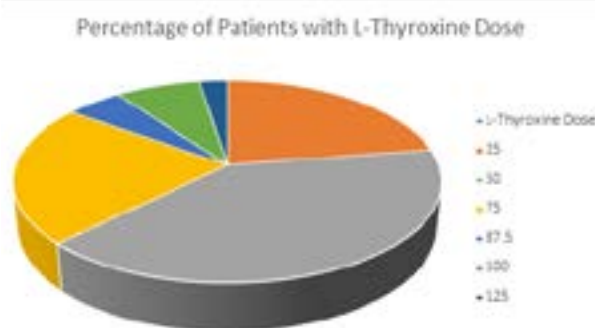
Adequacy of thyroid hormone replacement in a tertiary care
Jour of Diab and Endo Assoc of Nepal 2021; 5 (1): (33-38)
ISSN Print 2594-3367   ISSN Online 2631-2107

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study from Singapore stating mean daily dose of levothyroxine was 1.1.mcg/kg[17]. In addition, this study also found that participants who were over replaced had a higher daily levothyroxine dose of 1.4 mcg/kg. Similarly this daily levothyroxine dose was 1.23 mcg/ kg in an Indian study[13].

Similar daily dose of levothyroxine in the euthyroid and under replaced group was seen in our study, similar to the study from Singapore, which suggests that the under replacement may be due to factors other than dosages, such as medication adherence and decreased bioavailability. However no participants reported non adherent in this study; in contrast it was 10% in an Indian study[13] and 51.5% in another study[17].

Strength and limitations
To the best of our knowledge, this is the first study from Nepal on treatment outcome of primary hypothyroid patients. It highlighted the actual scenario of treatment outcome of primary hypothyroidism especially the magnitude of levothyroxine under and over replacement among this population. This study can be regarded as a pilot study especially on advocating the daily replacement dose of levothyroxine among Nepalese population.

Nevertheless, it has limitations. This is a cross sectional study and only provides a snapshot of the state of the management of condition, so it can not reflect the dynamic nature of the clinical practices amongst the physicians to achieve euthyroidism. Likewise, small sample size and only enrolling patients from a tertiary hospital may not be the representative data of Nepal.

Conclusion
Treatment of hypothyroidism with levothyroxine being most effective, easily available, simple regimen and not costly, still one third of patients are not meeting the treatment outcome. However, being the pioneer study from Nepal, this study suggests improved treatment outcomes compared to similar studies from the other part of the world.

Conflicts of interest
The author declares there is no conflict of interest.

Declarations
List of abbreviations
TSH: Thyroid Stimulating Hormone
NHANES: National Health and Nutritional Examinations Survey
OPD: Outpatient Department
SPSS: Statistical Package for The Social Sciences
KUSMS IRC: Kathmandu University School of Medical Sciences Institutional Review Comitee
SD: Standard Deviation
OPD: Outpatient Department
SD: Standard Deviation
SLC: School Leaving Certificate
LDL: Low Density Lipoprotein
HDL: HIgh Density Lipoprotein
TG: Triglyceride
SBP: Systolic Blood Pressure
DBP: DIastolic Blood Pressure

Ethics approval
The study was conducted after the ethical approval from the Institutional Review Committee,Kathmandu University School of Medical Sciences. Participants were explained about the research detail, its significance, the benefit and harm in Nepali language before obtaining the consent, their queries were answered. A statement indicating that the participants have understood all the information in the consent form and are willing to participate voluntarily was obtained. Participants were able to withdraw from the study at any time without giving any reason during the study period. The confidentiality of participants was assured and code number was used in each interview schedule and name of the participants was not mentioned anywhere.

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Jour of Diab and Endo Assoc of Nepal 2021; 5 (1): (33-38)
ISSN Print 2594-3367   ISSN Online 2631-2107

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Prevalence of Vitamin B12 Deficiency In Patients With Type II Diabetes Mellitus On Metformin

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Abstract

Background: Diabetes Mellitus is one of the most encountered disease in our out patient department and metformin is the first drug of choice to treat Diabetes mellitus. As metformin is one of the cheapest drug many patients use these drug for long period of time with consultation and without consultations with doctors. Patients under long term metformin use are not aware of Vitamin B12 deficiency and its associated signs and symptoms. In Nepal due to poverty, lack of education and awareness on diabetes mellitus we doctors find much difficult to explain patients on the consequences of diseases. So I decided to do this study which could be much easier to explain patients on effect of metformin of vitamin B12 levels and the consequences life style modifications and supplement of Vitamin B12 to the patients. **Methods:** This is a Cross-Sectional Study done in the patients with Type 2 diabetes were selected based on inclusion and exclusion criteria. Basic biochemical investigation were send the lab of the National academy of medical science. Serum B12 assay were done. Vitamin B12 deficiency is defined as values <150pg/ml. Association between vitamin B12 deficiency with duration of metformin therapy, duration of diabetes, with age, sex were done. **Results:** The mean vitamin B12 level is low as the duration of metformin treatment increases. The sex, age relation with development of vitamin B12 deficiency was not significant. In my study out of 210 patients 107 patients were having severe vitamin B12 deficiency level and 63 patients had a borderline Vitamin B12 deficiency level which shows that the deficiency increases as per longer use of metformin, which shows prevalence of 50.95%. **Conclusions:** Vitamin B12 deficiency occurs in type 2 diabetes mellitus patients treated with long term metformin. The duration of metformin therapy significantly affects the development of vitamin B12 deficiency. As a treating physician we always need to explain our patients about the side effect of metformin and regular follow up and investigations must be done to early diagnosis of vitamin B12 deficiency to improve the quality of life.

Keywords: B12 deficiency, Diabetes Mellitus, Metformin.

Introduction

Metformin has long been considered the initial drug therapy choice in the treatment of type 2 diabetes mellitus (T2DM). When monotherapy is initially preferred to treat hyperglycemia, Metformin is the widely recommended and violet et al in 2012 mentioned that it is prescribed to 120 million patients with diabetes around the world[1-5].

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It was in 1971, Tomkin et al first wrote an article describing Metformin associated vitamin B12 malabsorbtion.[6] Metformin lowers Vitamin B12 level and is associated with Vitamin B12 deficiency has been document in various studies in the past.[7-14].How Metformin causes Vitamin B12 deficiency is not clear but it is said that it stimulate the small bowel bacterial overgrowth and by directly decreasing vitamin B12 absorption. Lui et all in 2006 and Toh et all in 2009 also stated same with one of the documented side effects of metformin is vitamin B12 deficiency but it is almost always overlooked and seldom investigated[15-16]. Metformin

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also alters the intracellular handling of calcium on terminal ileum which decreases the absorption of the vitamin B12 intrinsic factor complex, which is later supported by a study done by Bauman et al 2000 that administration of the calcium reverses metformin induced vitamin B12 deficiency.[17]

Most of the time vitamin B 12 deficiency was not thought in such clinical situation. There is no universal recommendation to supplement vitamin B12, especially in high risk populations. Studying the biochemical profile to detect vitamin B12 deficiency in these populations will provide useful data to support the need for supplementation. The Objectives was to assess the Vitamin B12 level in chronic metformin treated type 2 diabetic patients and to assess the relation between metformin therapy duration & development of vitamin B12 deficiency.

Materials and Methods

The patients included in this study were from the National academy of medical sciences from September 2018 to Feb 2019. This was a Cross sectional study done in Diabetic outpatient department, National Academy of Medical Sciences, Bir Hospital. The inclusion criteria was Type 2 Diabetic patients, who were on Metformin therapy for more than 18 months. The present study will be conducted at National academy of medical sciences, Bir Hospital, kathmandu, which is a tertiary care center. This study will screen around 263 patients both in-patients and out patients with T2DM on metformin therapy for Vitamin B12 deficiency. This study was done to examine the prevalence of vitamin B12 deficiency in patients with T2DM on metformin attending National academy of Medical sciences,Bir Hospital.

The Exclusion Criteria was the Patient diagnosed with Pernicious anaemia, Malabsorbtion (coelic disease, Inflammatory disease, gastrointestinal surgery), Alcoholism, Malnutrition, Iron deficiency anaemia, history of thyroid disease and on thyroxine treatment and or a history of other organ specific autoimmune conditions(Vitiligo, addisons disease,

Hypoparathyroidism),Surgery involving small intestine or HIV infection. Intake of vitamin b12 or any multivitamin preparation during past 6 months

Results

Our study comprised of 263 type 2 diabetic population. Out of which 153 are males & 111 are females. The number of years patients were on metformin use is shown in Fig 1.
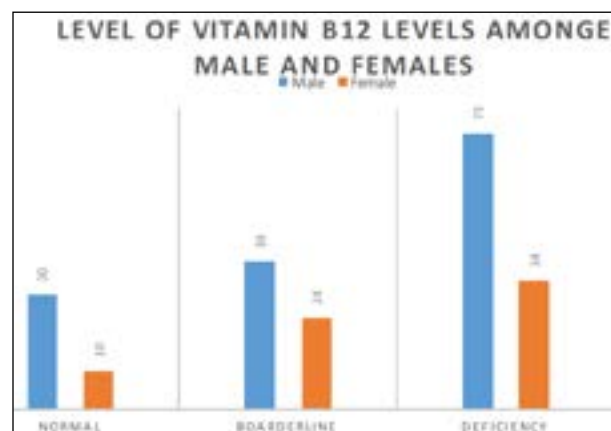
Fig 1: shows total number of years the patients
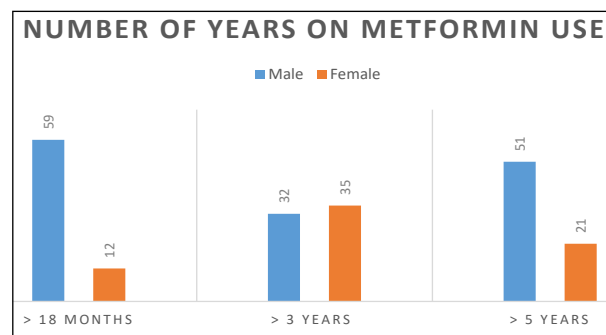
were on metformin use, which shows that as the number of year increases patients are using more Metformin.
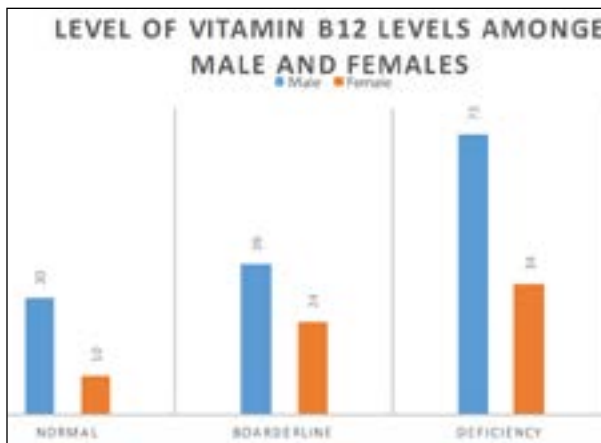
Among the study groups, the level of vitamin B12 among the male and females are shown in Fig 2. The relation between vitamin b12 deficiency and number of years on metformin use are shown in fig 3.

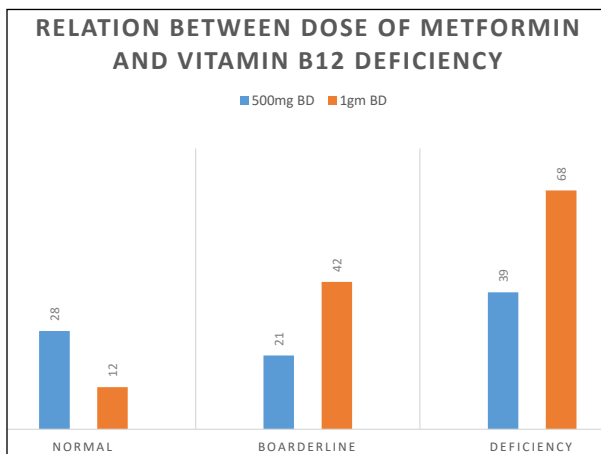*Fig 2: Chart shows the level of Vitamin B12 levels*

among male and female patients
Fig 3: Chart shows relation between Vitamin B12

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deficiency and number of years the patients using Metformin
Fig 4: Chart shows relation between dose of

Metformin and Vitamin B12 levels

Discussion

Metformin being the most commonly prescribed drug for the treatment of diabetes mellitus and there are proposed mechanism through which metformin interacts with vitamin B12 absorption, it causes deficiency of vitamin B12. It is a cross sectional study where the serum B12 level of type 2 Diabetic patients who are on metformin therapy (18 months) was measured and correlated with duration of metformin therapy, duration of diabetes mellitus.

After exclusion criteria as per use of Vitamin B12, Patients with CKD,Iron deficiency Anemia, long use of Alcohol use, past and recent history of Thyroid illness and past Gastrointestinal surgery 54 patients were excluded from the study. So 210 patients as 142 male and 68 females were included in the study.

71 patients were using metformin for more than 18 months, 67 for more than 3 years and 72 for more than 5 years, shows that metformin use also increases according to the increase in number of years of Diabetes.

In my study 107 patients were having severe vitamin B12 deficiency level and 63 patients had borderline Vitamin B12 deficiency levels which shows that the deficiency increases as per longer use of metformin. This value shows the prevalence of 50.95 %with vitamin B12 deficiency amonge patients on long term metformin use. Our study is also being supported by ting et al[24] and pierce et al[25]. with this results of my study I am much aware that care full followup of the patients with metformin on both high dose and low dose in very important and I must advice my patients for annually check up vitamin B 12 level,that I was not aware or is being neglected before due to poverty and irregular follow up of patients.

This study also shows that the dose of metformin also effects the level of Vitamin B12.As seen in our results 68 patients with severe Vitamin B12 were on Metformin 1gm on twice daily basis. Our study is also being supported by ting et al.[24]

As we see increased prevalence of vitamin B12 deficiency,we can also recommend annual screening for vitamin B12 and supplementation should be adopted among diabetic patients with specific risk factors of vitamin B12 deficiency which is also supported by kribirige D and Mwebeze R in 2013.[26]

The prevalence of Vitamin B12 defiency in Patients with T2DM on metformin therapy in Nepal is unknown and the measurement of serum Vitamin B12 in T2DM is not a part of the standard annual

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review examination. Many studies were done in the past and showed that prevalence of Vitamin B12 deficiency varied greatly and ranged between 5.8% and 52 %.[27-35]

Conclusion

In a country like Nepal where most of the patients coming to our out patient department are from remote areas of Nepal, we as a treating physician must explain our patients about the possible side effects of Metformin, which is one of the mostly used drug and patients use metformin for long period of time without consulting the doctors. Chronic use of metformin causes symptomatic and asymptomatic vitamin b12 deficiency.

Vitamin B12 assay in the patients who were on chronic metformin therapy helps in assessing Vitamin B12 deficiency.
The duration of metformin therapy has affected the vitaminB12 status significantly.

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CASE REPORT

Hypogonadotropic-hypogonadism (Kallman Syndrome) in Young Adult

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Abstract

Background: Kallmann syndrome (KS) is a rare disorder first described in 1856 and later studied by Kallmann in 1944 [1]. It is now designated as olfactogenital dysplasia with an association between agenesis of the olfactory bulbs and hypogonadism. The prevalence of KS is still unknown. The reported incidence is 1 in 8000 to 1 in 10 000 in men and rare in women[2]. More than 24 genes are underlying KS that have been identified[3]. Mutations in these genes are thought to interfere with the expression of cell markers that guide migrating neurons, leading to failed migration of GnRH neurons and olfactory neurons to the forebrain during fetal development. The main clinical characteristics of KS include hypogonadotropic hypogonadism and anosmia or hyposmia. Less common phenotypes include cardiovascular anomalies, unilateral renal agenesis, cleft palate and cleft lip, cryptorchidism and osteoporosis [4]. Magnetic resonance imaging (MRI) can show abnormalities of the olfactory system and other forebrain structures[5]. Other exceptions may be discovered using MRI because of its high resolution and multiplanar capabilities, such as pituitary abnormalities[6].

Key words: Hypogonadotropic-hypogonadism, Kallmann syndrome, olfactogenital dysplasia.

Case Presentation

An 18-year-old male patient presented to our hospital with complaints of childish voice. He was born to a nonconsanguineous marriage, full-term normal vaginal delivery. He has three siblings, and all are healthy. At birth, micropenis was observed but took no further action. He went circumcision at the age of one year. His development was apt and passed in schools with flying colours. In high school, he was bullied by his classmates for his voice. He also noted decreased ability to smell and absent morning erections. He has no history of vision difficulty, difficulty in hearing, seizures and movement disorders. No significant family history from both parental sides.

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On examination, his height was 160cm, weight of 55kg, arm span of 165cm with the upper segment to lower segment ratio of 1.1:1. He has a high pitch voice. He has no moustache, beard, absent hair over the axilla and pubic region. He has bilaterally descended testes with a pre-pubertal size of around 1 cm and a penile length of 1.8cm. On general examination, he has pallor. His systemic examination was remarkable for the reduced smell.

Photographs showing before treatment and after testosterone therapy

Hypogonadotropic-hypogonadism (Kallman syndrome) in young adult
Jour of Diab and Endo Assoc of Nepal 2021; 5 (1): (43-45)
ISSN Print 2594-3367   ISSN Online 2631-2107

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A complete haemogram was significant for anaemia (Hb- 11.5gm/dl). His serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone revealed hypogonadotropic hypogonadism and tabulated below.

Hormones	Patient values	Reference range
Serum FSH	0.33 mIU/ml	1–10.5 mIU/ml
Serum LH	0.13 mIU/ml	1.9–9.4 mIU/ml
Serum testosterone	100ng/Dl	

FSH, follicle-stimulating hormone; LH, luteinizing hormone.

On Imaging , Ultrasound abdomen revealed the normal study. Scrotal ultrasound showed bilateral small testis size and volume (2ml). MRI brain showed hypoplastic olfactory bulbs.

The patient was started on parenteral testosterone supplements to improve his secondary sexual characters. The patient was being followed up regularly every three months. Follow up demonstrated improvement in anaemia, voice, phallic size, and development of sexual characters.

Discussion

KS is an isolated form of hypogonadotropic hypogonadism in combination with a defect in the sense of smell. Due to flaws in olfactory structures (bulbs, grooves, tracts) and altered GnRH-secreting neurons' migration into the preoptic and hypothalamic regions[7]. It is a genetically heterogeneous disease inherited in an X-linked, autosomal dominant or autosomal recessive pattern. The most prevalent is an X-linked form that charts to the KAL1 gene, which encodes for a neuron adhesion molecule believed to be accountable for guiding the migration of LH-releasing hormone-secreting neurons to the medial basal hypothalamus.

Our outpatient manifested with delayed puberty, characterized by high pitched voice, absence of facial and axillary hair and sparse pubic hair, micropenis and bilateral small testes. The hormonal evaluation showed low FSH, low LH and low testosterone levels. A diverse group of disorders with varied pathophysiology comprise hypogonadotropic hypogonadism or hypothalamic-pituitary hypogonadism. Examples include an isolated abnormality in hypothalamic GnRH, isolated abnormality in pituitary gonadotropins (LH, FSH) and conditions in which both hypothalamic and pituitary dysfunction is present. The differential diagnosis will include KS, GnRH receptor mutation, GPR54 mutation, DAX-1 mutation and hypopituitarism[8].

In this case, the diagnosis of KS is straightforward because of the hypogonadotropic hypogonadism in association with hyposmia and documented radiologic findings in MRI.

Morphological anomalies of the olfactory apparatus in KS are best evaluated with MRI. Cranial MRI, in our case, revealed a hypoplastic bilateral olfactory bulb. The pituitary gland is normal.

Clinical diagnosis of KS in adults is reasonably apparent, depending on the co-existence of anosmia with subnormal levels of gonadal steroid and gonadotropins. However, the diagnosis may be difficult to establish in pre-pubertal age patients who may require genetic testing and MRI[9].In these patients, MRI will aid in the diagnosis of KS by demonstrating characteristic abnormalities in olfactory sulci and tracts. To diagnose KS, infiltrative disorders and space-occupying lesions of the pituitary must be excluded. Novel researches have revealed ethmoid bone anomalies and pituitary aberrations on computed tomography in KS patients.

Therapeutic objects in the adolescent male with CHH are well defined: to produce virilization, to reach optimal adult height, to acquire average bone mass and body composition, to achieve normal psychosocial development, and to gain fertility. Gonadotropins are used for fertility treatments in

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adult patients with CHH and can also stimulate pubertal maturation in adolescent males with CHH. An additional advantage of gonadotropin treatment compared with T treatment is the stimulation of testicular growth and spermatogenesis. Therefore, gonadotropin therapy may contribute to crucial psychical reassurance in teenagers and heighten self-confidence[10].

In summary, we have a KS case who presented with a micropenis early in life but unfortunately was not further evaluated. He subsequently presented with eunuchoid body proportion, high pitched voice, absence of facial and axillary hair and sparse pubic hair, micropenis and bilaterally descended pre-pubertal testes. Associated findings were hyposmia and facial anomalies, namely congenital absence of puncta and smooth philtrum. The hormonal evaluation was consistent with hypogonadotropic hypogonadism. Cranial MRI showed aplastic right olfactory bulb and hypoplastic left olfactory bulb.

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