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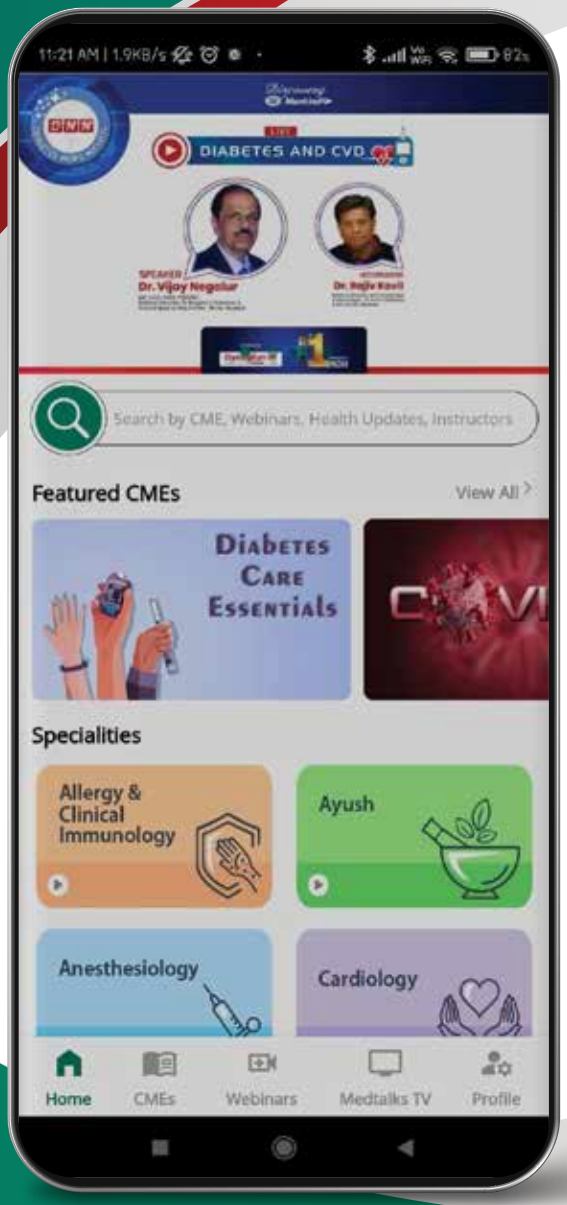

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REVIEW ARTICLE

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CASE REPORT

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Insulin is Essential: The National List of Essential Medicines, India, 2022

Introduction

Insulin is essential for life. While most persons produce adequate amounts of insulin, not everyone is lucky enough. Persons living with type 1 diabetes, with pancreatic diabetes, and with severe or long-standing type 2 diabetes need exogenous insulin for survival.[1] Many persons with type 2 diabetes and comorbidities such as renal or hepatic impairment, severe sepsis or infection, also require insulin. Insulin is also the drug of choice for glycemic control during pregnancy. Unfortunately, however, insulin is expensive, and may be out of reach of many people who need it.[2] One way of ensuring affordable insulin is to declare it an essential drug.

India's National List of Essential Medicines

The National List of Essential Medicines (NLEM), India reflects this thought process. Successive editions of the NLEM have included various preparations and strengths of insulin.[3,4] This year's NLEM lists four insulins: soluble, NPH (neutral protamine Hagedorn) premixed insulin and glargine, irrespective of delivery device.[5] It is assumed that all strengths (40 IU/mL and 100 IU/mL for human insulin, and 100 μ/mL for glargine) are included in the essential list. The 50:50 premixed insulin preparation is not included in NLEM, though it must be admitted that it is not as commonly prescribed as the 30:70 preparation.

The addition of insulin glargine in the Indian NLEM is a welcome development. This underscores the acceptance of the need to provide safe and effective medication to persons living with diabetes at an affordable cost. The updated NLEM highlights India's commitment towards providing world-class treatment to its citizens, and towards ensuring that the noncommunication disease epidemic is addressed aggressively. The Indian pharmaceutical industry has contributed immensely to the production of economical and efficient insulin, not only for the domestic, but also for the global market.[6] An Indian insulin glargine brand has received a label for interchangeability with originator brands from the United States Food and Drug Administration (US FDA),[7] it implies the quality, robustness in clinical data and more importantly "a make

in India product to the global need" which addresses two key barriers, i.e., affordable and accessible insulin to all. US FDA defines Interchangeable if the biological product "is biosimilar to the reference product" and "can be expected to produce the same clinical result as the reference product in any given patient."[8] The 'interchangeable' status can prompt faster and wider uptake of insulin biosimilars and keep the insulin expenditure under control, especially for patients who otherwise practice nonadherence or rationing of life-saving insulin.

National Lists of Essential Devices and Essential Diagnostics

Persons living with diabetes need much more, however. Just as insulin preparations are essential, so are insulin delivery devices like syringes, pens and pumps.[9] Insulin monitoring systems, such as glucose monitors, urine sugar strips, ambulatory/continuous glucose monitoring systems are equally essential to ensure safe and accurate therapy. Equal emphasis should therefore be placed on diabetes care in the National Lists of Essential Devices and Essential Diagnostics.

Noninsulin Medications

The 2022 NLEM contains a brief, yet comprehensive, list of noninsulin oral medications.[5] Their listing reflects the increasing disease burden of diabetes, as well as the efficacy, safety and cost-effectiveness of the drug. Teneligliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor has been added this year. The sulfonylurea glimepiride, and the insulin sensitizer, metformin, complete the list. No sodium-glucose co-transporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 receptor agonists (GLP-1RA) figure in the list, however.

Summary

As we work towards becoming the Diabetes Care Capital of the world (Prof BK Sahay, personal communication), each and every stakeholder's involvement is important. Diabetes care cannot be achieved without ensuring availability, accessibility and affordability of diabetes related diagnostics, drugs and devices. The NLEM 2022 demonstrates the commitment of the Indian government towards achieving this goal. Sustained and concerted efforts will be needed in the future as well, to accomplish our goals.

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ORIGINAL ARTICLE

Diabetes Risk Score in Indian Population: Experience from Central India

JAIDEEP KHARE*, HARSHA PAMNANI†, ANUVRAT BHATNAGAR‡, SHAIFALI BANSAL#, SUSHIL JINDAL¥

*Associate Professor
†Assistant Professor
‡Senior Resident
Dept. of Endocrinology
#Professor, Dept. of Medicine
¥Professor and Head, Dept. of Endocrinology
People's College of Medical Sciences and Research Centre, Bhopal, Madhya Pradesh

A B S T R A C T

Introduction: Diabetes is a major health problem in the world causing significant morbidity and mortality. Currently, 77 million people in India and 463 million people are living with diabetes across the world, and this number is expected to rise to 101 million in India and 578 million globally by 2030. The key to reduce the morbidity and mortality is early diagnosis and management. The Madras Diabetes Research Foundation (MDRF) has developed an Indian Diabetes Risk Score (IDRS) to identify people who are at risk of developing diabetes or are undiagnosed. Thus, we conducted a study to calculate the IDRS of people from Central India and identify those who are at risk of getting diabetes. **Methods:** A total of 1,500 patients or attendants, aged 18 to 60 years (mean age 41.2 years), visiting the Endocrinology clinic, and not diagnosed with diabetes earlier were included in the study after taking proper consent and IDRS was calculated. **Results:** The male-to-female ratio was 914:586. The mean IDRS was 51.29 in our population with 35.93%, 18.2% and 45.87% of screened subjects having a score of <30, 30-60 and ≥60, respectively. **Conclusion:** Forty-five percent people of the population was at high risk of diabetes as estimated by IDRS, which proved to be an effective and economical tool to identify persons at increased risk of diabetes and diagnose the undiagnosed cases and start early management to reduce the morbidity and mortality.

Keywords: Diabetes, Indian Diabetes Risk Score, Madras Diabetes Research Foundation

Introduction

Diabetes is a major health problem in the world leading to considerable morbidity and mortality. Prevalence of diabetes is expected to rise exponentially, currently 77 million people in India and 463 million people are living with diabetes across the world, and this number is expected to rise to 101 million in India and 578 million globally by 2030 which could mostly be attributed to unhealthy lifestyle, increasing life expectancy, illiteracy, lack of awareness and low socioeconomic status.[1] The key to reducing the morbidity and mortality is early diagnosis and management. The Madras Diabetes Research Foundation (MDRF) has developed an Indian Diabetes Risk Score (IDRS) to identify people who are at risk of developing type 2 diabetes or are yet undiagnosed.[2]

Thus, we conducted a study to calculate the IDRS of people from Central India and identify those who are at risk of getting diabetes or those who are not diagnosed with diabetes using IDRS.

Address for correspondence
Dr Jaideep Khare
Associate Professor, Dept. of Endocrinology
People's College of Medical Sciences and Research Centre, Bhopal, Madhya Pradesh
E-mail: drjaideepkhare919@gmail.com

Material and Methods

This was an observational cross-sectional study conducted at our Endocrine Outpatient Department (OPD).

All patients or attendants visiting the Endocrinology OPD, willing and not diagnosed with diabetes earlier were included in the study after taking proper informed consent. Patients who were critically ill, pregnant, had history of diabetes or not willing to participate in the study were excluded.

A total of 1,500 volunteers were enrolled who met the inclusion criteria and IDRS was calculated as described in Table 1. We also recorded the random capillary glucose levels with glucometer and correlated it with IDRS. Glucometer reading of more than 140 mg/dL was considered deranged.

Results

One thousand five hundred volunteers, aged between 18 and 60 years (mean age 41.2 years) were included in the study. The male-to-female ratio was 914:586.

The mean IDRS in our study population was 51.29. Details of various risk factors are described in Table 1. And, 35.93%, 18.2% and 45.87% of the screened volunteers had a score of <30, 30-60 and ≥60, respectively (Table 2). Seven (1.29%), 23 (8.42%), 268 (38.95%) volunteers were identified with deranged blood glucose levels with IDRS of <30, 30-60 and ≥60, respectively (Table 3).

Discussion

Diabetes is a major health problem in the world. Early diagnosis and management can reduce the associated morbidity and mortality by preventing complications related to diabetes. There is a perceived need for a tool, which is not only economical but also socially acceptable and reliable to identify persons at risk of diabetes. MDRF has developed the IDRS, which has all the above-mentioned qualities to identify people who are at risk of developing diabetes or are undiagnosed type 2 diabetes. IDRS identified people as low-risk, moderate-risk or high-risk if score was <30, 30-60 or ≥60, respectively.

Hence, we calculated the IDRS in our population and identified the prevalence of various components of IDRS and correlated it with glucometer readings

Table 1. Prevalence of Various Risk Factors in Our Study Population

	Score	Male (n = 914)	Female (n = 586)	Total (n = 1,500)
Age (years)				
<35	0	281	207	488
35-49	20	343	224	567
≥50	30	290	155	445
Abdominal obesity				
Waist circumference (cm)				
<80 Female, <90 Male	0	401	145	546
80-89 Female, 90-99 Male	10	348	237	585
>90 Female, >100 Male	20	165	204	369
Physical activity				
Exercise (Regular) + Strenuous exercise	0	121	86	207
Exercise (Moderate)	10	387	149	536
Exercise (Mild)	20	147	291	438
No	30	259	60	319
Family history of diabetes				
No	0	134	175	309
1 Parent	10	568	281	849
Both parent	20	212	130	342
Maximum score	**100**	**51.25**	**51.37**	**51.29**

Table 2. Distribution of the Study Population According to the Risk Score

Score	Male (%)	Female (%)	Total (%)
<30	326 (35.76)	213 (36.34)	539 (35.93)
30-60	161 (17.62)	112 (19.11)	273 (18.20)
≥60	427 (46.72)	261 (44.45)	688 (45.87)
Total	**914**	**586**	**1,500 (100)**

Table 3. Correlation Between IDRS and Deranged Blood Glucose Profile

Score	N (%)	Deranged blood glucose (RBS >140 mg/dL or FBS >100 mg/dL with glucometer [% of cases])
<30 (Low)	539 (35.93)	7 (1.29)
30-60 (Moderate)	273 (18.20)	23 (8.42)
≥60 (High)	688 (45.87)	268 (38.95)

for capillary glucose levels. In our study, the mean IDRS was 51.29 suggesting that our population is at moderate-risk for diabetes; 35.93%, 18.2% and 45.87% of screened volunteers had a score of <30, 30-60 and ≥60, respectively.

Nandeshwar et al in their study in 2010 identified 2.80% subjects as low-risk, 28.40% as moderate-risk and 68.80% as high-risk as per the IDRS.[3] This increase in low- to moderate-risk group and decrease in high-risk group population may be because of increasing awareness among people regarding diabetes and its complications due to several awareness programs and activities conducted by medical fraternity.

Seven (1.29%), 23 (8.42%), 268 (38.95%) volunteers were identified with deranged blood glucose levels with IDRS of <30, 30-60 and ≥60, respectively. Our findings were also in concordance with those of Mohan et al, which suggested that only 43% population with IDRS ≥60 need to be screened for diabetes, which will help in significant reduction in financial burden.[2]

Conclusion

Forty-five percent people of our population is at high risk of diabetes as estimated by IDRS, which is an effective and economical tool to identify the people who are at increased risk of diabetes and diagnose undiagnosed people with diabetes.

Thus, we recommend regular use of IDRS to identify people at increased risk of diabetes and screen them for diabetes and its complications to start early management and reducethe diabetes-related morbidity and mortality.

Limitation of Study

Possibility of sample bias cannot be ruled out as volunteers were from single tertiary care center.

Conflict of Interest

Declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

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ORIGINAL ARTICLE

Insulin Initiation with Insulin Degludec/Insulin Aspart versus Insulin Glargine in Oral Antidiabetic Drugs Failure Patients with Type 2 Diabetes Mellitus: A Real-World Study from India

SANJAY CHATTERJEE*, SOUMYABRATA ROY CHAUDHURI†, ANIRBAN MAJUMDER†, DEBMALYA SANYAL†

*Apollo Gleneagles Hospital, Kolkata, West Bengal
†Dept. of Endocrinology, KPC Medical College, Kolkata, West Bengal

ABSTRACT

Context: Oral antidiabetic drug (OAD) failure is an indication for starting insulin therapy, but there is still a dilemma as to whether basal insulin or a premixed/co-formulation analog should be the choice. **Aim**: To compare the safety and efficacy of once daily (OD) insulin degludec/insulin aspart (IDegAsp) to OD insulin glargine (IGlar U100) in insulin-naïve Indian subjects with type 2 diabetes mellitus (T2DM), inadequately controlled with OADs alone. **Setting and design**: Retrospective study. **Methods and material**: Data was retrieved from the author's clinic database of OAD failure patients (18-80 years), who were started either with (IGlar U100, n = 120) or IDegAsp (n = 89) OD over and above the standard of care. Data of fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycated hemoglobin (HbA1c) from baseline and at last follow-up visits were collected. **Statistical analysis used**: Baseline characteristics and change in study parameters during the follow-up period were computed between two groups (IGlar U100 vs. IDegAsp) by unpaired *t*-test and paired *t*-test, respectively. ANCOVA test was used to compute percentage reduction in body weight, body mass index (BMI), FPG, PPG and HbA1c in between two groups (IGlar U100 vs. IDegAsp). **Results**: IDegAsp caused a significantly greater reduction in FPG, PPG and HbA1c as compared to the IGlar U100 arm. There was no significant difference in the proportion of patients with hypoglycemia between IDegAsp and IGlar U100 groups (p = 0.208). No episodes of severe hypoglycemia were reported. **Conclusion**: Comparison of IDegAsp and IGlar U100 OD in T2DM patients indicated that both were relatively safe but the former controlled FPG and PPG levels more effectively.

Keywords: Oral antidiabetic agent, insulin, hypoglycemia, type 2 diabetes mellitus, India

Introduction

Currently, 573 million people are living with diabetes globally. There is a worldwide increase in the prevalence and incidence of diabetes which is predicted to rise to 643 million by 2030. In India, the number of adults with diabetes in 2021 was 74.2 million which is expected to exceed 124 million by 2045.[1] Several national and international guidelines on the treatment of type 2 diabetes mellitus (T2DM) exist.[2-5] As per all the national and international guidelines, oral antidiabetic drug (OAD) failure is an indication for starting insulin therapy. It can be defined as a clinical situation where glycated hemoglobin (HbA1c) remains above goal, despite concurrent use of an optimum dose of three or more glucose-lowering drugs

Address for correspondence
Dr Soumyabrata Roy Chaudhuri
Dept. of Endocrinology, KPC Medical College, Kolkata, West Bengal
E-mail: Soumya.academics@gmail.com

of different classes, one of which should be metformin and the second, preferably a sulfonylurea, provided adequate diet and exercise have been followed, and comorbid conditions causing hyperglycemia have been ruled out.[6] Nevertheless, there is still a dilemma as to whether basal insulin or a premixed/co-formulation analog should be the choice for initiation.

Insulin treatment is administered as an injection of basal insulin or a combination of bolus and basal insulins. Insulin degludec/insulin aspart (IDegAsp) is a soluble combination of insulin degludec (IDeg), an ultra-long-acting basal insulin and the rapid-acting insulin analog, insulin aspart (IAsp). Within the IDegAsp formulation and after subcutaneous injection, independent pharmacokinetic/pharmacodynamic characteristics of the components are maintained.[7] IDeg has a flat and stable glucose-lowering effect that results in a much longer duration of action (>42 h), and four times lower pharmacodynamic variability than insulin glargine (IGlar U100) under steady-state conditions.[8-10] This in turn results in a lower risk of hypoglycemia, particularly nocturnal hypoglycemia with IDeg, a distinct clinical advantage over other basal insulin.[11,12] In T2DM, IDegAsp once daily (OD) has been analyzed as initiation as well as intensification strategy. IDegAsp can be initiated in either OD or twice daily (BID) doses based on the clinical situation, as monotherapy or together with metformin. T2DM patients switching from OD basal or premix insulin therapy can be converted unit-to-unit to IDegAsp OD at an equivalent previous total daily insulin dose.[13,14] IDegAsp has been shown to provide significant reductions in fasting plasma glucose (FPG), the total daily dose of insulin, and rate of overall and nocturnal hypoglycemia as compared to biphasic insulin.[15]

To suit Indian reality of diabetes management (such as high carbohydrate diet), guidelines and recommendations need to be adapted.[16,17] Thus, consensus on initiation and intensification of premix insulin in the management of T2DM recommends premix insulin/co-formulation for effective and accessible glycemic control (predominantly postprandial hyperglycemia).[18] This real-world study aimed at comparing the safety and efficacy of IDegAsp OD to that of IGlar U100 OD in insulin-naïve Indian subjects with T2DM insufficiently controlled with oral antidiabetic medicines alone.

Subjects and Methods

Data was retrieved from the author's clinic database of OAD failure patients (18-80 years) who were started on basal insulin (IGlar U100, n = 120) or IDegAsp (n = 89) OD over and above the standard of care. The data of FPG, postprandial plasma glucose (PPG) and HbA1c from baseline and at last follow-up visit was collected for analysis.

Key eligibility criteria for study consisted of the following:

Inclusion Criteria

- Indian insulin naïve adults with T2DM.
- Age 18 to 80 years.
- On stable optimal dose of 3 OADs for last 90 days.
- HbA1c <11%.

Exclusion Criteria

- Type 1, gestational diabetes mellitus (GDM) and other types of diabetes.
- Pregnancy and lactation.
- Requiring insulin as rescue medication due to intercurrent illness in last 3 months.
- Incomplete dataset and irregular intake of history of insulin.
- Faulty injection technique.

All patients visiting the author's outdoor clinic from 1st January 2019 to 30th October 2019 were assessed for the type of diabetes therapy. Patients who had been on basal insulin (IGlar U100) or IDegAsp, OD for 35 weeks or more were included in the study. Informed consent was obtained from all subjects. Details were collected regarding basic demographics, dosage, frequency of insulin, body weight, blood pressure and glycemic control. Indications for the use of IGlar U100 and IDegAsp were recorded. Data is expressed using descriptive statistics as mean ± SEM (standard error of the mean), wherever applicable. Data was analyzed using SPSS/Microsoft Excel software. Baseline characteristics and changes in study parameters during the follow-up period were compared between two groups (IGlar U100 vs. IDegAsp) by unpaired *t*-test and paired *t*-test, respectively. Analysis of covariance (ANCOVA) test was used to compare the percentage change in body weight, body mass index (BMI), FPG, PPG and HbA1c between two groups (IGlar U100 vs. IDegAsp). Data at baseline, 35.56 ± 25.97 weeks (IGlar U100 cohort), and 28.53 ± 19.63 weeks (IDegAsp cohort) was used for analysis.

Assessment

Subjects were treated with either IDegAsp or IGlar U100 OD, using stratification (by previous OAD treatment). The IDegAsp dose was administered subcutaneously

just before the largest meal of the day and IGlar U100 (Lantus®, SoloSTAR®, Sanofi-Aventis, Frankfurt, Germany) was administered according to the approved labeling (either before breakfast or at bedtime).

Results

The baseline demographics and clinical parameters were found to be comparable, except for body weight that was nonsignificantly higher in the IGlar U100 arm and hence required a higher insulin dose. The mean (±SD) duration of follow-up was 35.56 ± 25.97 weeks in IGlar U100 cohort and 28.53 ± 19.63 weeks in IDegAsp cohort and this difference was nonsignificant (p = 0.104). The glycemic triad, i.e., FPG, PPG and HbA1c was significantly reduced from baseline in both the arms (Table 1). However, IDegAsp caused statistically significant greater reduction in FPG, PPG and HbA1c as compared to the IGlar U100 arm. Three patients of IGlar U100 complained of injection site burning but no such adverse events were reported in the IDegAsp arm. There were overall 18 episodes of hypoglycemia in the IGlar U100 group and 10 episodes in the IDegAsp group. Though the proportion of patients with hypoglycemia was higher in IGlar U100 group as compared to IDegAsp group, the difference failed to reach any statistical significance (p = 0.208; Chi-square test). Severe hypoglycemia episodes were not reported.

Eighty-nine subjects (53 men and 36 women; mean age 59.49 ± 3.31 years) received IDegAsp and, 120 subjects (71 men and 49 women; mean age 61.88 ± 10.87 years) who received IGlar U100 treatment had completed the duration of 26 weeks or more. Fall in HbA1c from baseline to follow-up visit was 9.61 ± 0.78% to 8.56 ± 0.18% in the IGlar U100 cohort, and from 9.61 ± 2.12% to 8.02 ± 1.02% in the IDegAsp cohort. Mean percentage reduction in the IDegAsp cohort was found to be -16.55 ± 4.07 and was statistically significant (p = 0.044) compared -9.88 ± 2.22 in the IGlar U100 cohort.

FPG decreased from 230.69 ± 7.49 mg/dL to 154.78 ± 7.59 mg/dL (IGlar U100 cohort), from 236.08 ± 86.31 to 134.31 ± 51.40 (IDegAsp cohort) and was found statistically significant (p < 0.001). Mean percentage

Table 1. Baseline Characteristics of the Patients

	IGlar U100 (n = 120)	IDegAsp (n = 89)	P (*t*-test)
Male, n (%)	71 (59.17)	53 (59.55)	0.629
Female, n (%)	49 (40.83)	36 (40.45)	
Age (years), Mean ± SEM	61.88 ± 10.87	59.49 ± 3.31	0.816
Body weight (kg), Mean ± SEM	69.65 ± 2.13	68.51 ± 11.88	0.716
SBP (mmHg), Mean ± SEM	132.22 ± 2.21	130.65 ± 2.28	0.487
DBP (mmHg), Mean ± SEM	80.56 ± 1.31	78.97 ± 1.73	0.943
BMI (kg/m^2), Mean ± SEM	26.78 ± 3.22	26.97 ± 2.19	0.865
FPG (mg/dL), Mean ± SEM	230.69 ± 7.49	236.08 ± 86.31	0.206
PPG (mg/dL), Mean ± SEM	295.18 ± 11.75	309.06 ± 106.76	0.578
HbA1c (%), Mean ± SEM	9.61 ± 0.78	9.61 ± 2.12	0.385
Insulin dose (IU), Mean ± SEM	13.44 ± 0.41	10.23 ± 1.41	0.001
Insulin dose/kg body wt. (IU), Mean ± SEM	0.20 ± 0.18	0.14 ± 0.09	0.032
LDL cholesterol (mg/dL), Mean ± SEM	90.01 ± 3.99	81.31 ± 4.86	0.039
Serum creatinine (mg/dL), Mean ± SEM	0.95 ± 0.03	1.01 ± 0.33	0.701

SEM = Standard error mean; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; BMI = Body mass index; FPG = Fasting plasma glucose; PPG = Postprandial plasma glucose; HbA1c = Glycated hemoglobin; LDL = Low-density lipoproteins.

P < 0.05 considered as statistically significant, p computed by unpaired *t*-test.

reduction was -33.04 ± 8.61 (IGlar U100 cohort) and -34.63 ± 9.12 (IDegAsp cohort) with p-value 0.041.

Mean percentage reduction in PPG was -20.34 ± 2.89 (IGlar U100 cohort) and -41.53 ± 4.76 (IDegAsp cohort) with p-value 0.036. PPG decreased from 295.18 ± 11.75 mg/dL to 236.37 ± 10.58 mg/dL (IGlar U100 cohort) and from 309.06 ± 106.76 to 180.76 ± 55.09 (IDegAsp cohort) and was found statistically significant ($p < 0.001$). Mean insulin dose/kg body weight at the end of 26 weeks was significantly lower for patients treated with IDegAsp (0.23 ± 0.22) than IGlar U100 (0.42 ± 0.57), ($p = 0.010$).

Discussion

In this Indian real-world evidence study of 26 weeks, IDegAsp administered OD significantly improved HbA1c levels as compared to IGlar U100 OD. While this analysis is retrospective, not controlled, and is limited by the fact that dropouts were not studied, it does add value to existing literature. It must be noted that this study was performed in a nonreimbursed environment, where patients have to pay from their pocket for insulin and other supplies.

A multicenter, prospective, noninterventional, preference study was conducted with T2DM patients (n = 505) in India, with biphasic insulin aspart 30/70 (BIAsp 30). After 12 weeks of treatment, 96.4% of patients were willing to pay for BIAsp 30. Significantly improved mean treatment and device satisfaction was reported from baseline as well ($p < 0.0001$).[19]

As IDegAsp comprises rapid-acting insulin aspart and ultra-long-acting IDeg, it allows control over both FPG and PPG levels. IDegAsp provides advantages in dose titration, dose timing flexibility, treatment intensification (from OD to BID dose adjustments), lower injection burden, easy switching and lower hypoglycemia risk. IDegAsp and other antihyperglycemic drugs can be co-administered; however, sulfonylureas need to be stopped or their dose reduced. On the other hand, dose of IDegAsp may need to be lowered upon the addition of glucagon-like peptide-1 receptor agonists or sodium-glucose co-transporter-2 inhibitors.[13,14] In a 12-week follow-up study with treatment-naïve, recently diagnosed T2DM Indian patients (n = 41), Chaudhuri et al observed a significant improvement in FPG, PPG and HbA1c over the study period with 85.4% of patients receiving OD IDegAsp (10 units) + metformin extended-release (1 g/day).[20] Only 2 patients were reported for symptomatic hypoglycemia and none for severe or nocturnal hypoglycemia. Weight changes were nonsignificant. Conclusively, IDegAsp (OD or BID) was safe and effective for treatment-naive Indian patients.

In a 16-week long exploratory study, it was found that IDegAsp was able to achieve target HbA1c <7.0%, without confirmed hypoglycemia in 67% of subjects (who were poorly controlled on metformin). The daily dose requirement of IDegAsp was 0.57 ± 0.23 U/kg and was 13% lower than that of BIAsp 30. In this study, significantly lower FPG and lower rate of confirmed hypoglycemia were noted with IDegAsp.[21] Another 26-week long Asian study observed a lower dose requirement of IDegAsp OD (0.79 U/kg), as compared to BIAsp 30, in controlling HbA1c, with lower FPG and similar (low) risk of severe hypoglycemia.[22]

Effective glycemic control was achieved including achievement of target HbA1c levels (8.02 ± 1.02%) with IDegAsp, after 26 weeks of treatment, with a percentage reduction -16.55 ± 4.07 in the IDegAsp cohort compared to -9.88 ± 2.22 in the IGlar U100 cohort ($p = 0.044$) (Table 2). Superior reduction in HbA1c was seen with OD IDegAsp as compared to OD IGlar U100 in a 26 weeks randomized controlled trial wherein patients in the OD IDegAsp arm took it before the major meal.[23] In this study, participants on IDegAsp received relatively lower mean total insulin dose compared with those on IGlar U100. Patients receiving IDegAsp were able to reduce their FPG levels (134.31 ± 51.40) to a greater extent than with IGlar U100 (154.78 ± 7.59) $p < 0.001$, while receiving lower insulin dose (Table 2), suggesting that the glucose-lowering effects of IDeg are preserved in IDegAsp. A nonsignificant increase in mean body weight was observed in patients at 26 weeks associated with IDegAsp. IDegAsp provided significant control as compared to IGlar U100 in reducing the PPG increment. Monnier et al[24] had reported that reduction of PPG excursions has profound effects on long-term glycemic control once FPG has reached the target. The results of this real-world study support this observation as we find a larger reduction in HbA1c with IDegAsp while, the reduction in FPG was similar in both treatment groups after 26 weeks (Table 3).

Both treatments had similar safety profiles. Findings demonstrate that IDegAsp results in a lower rate of hypoglycemia compared with IGlar U100 when using this threshold in the Indian population.[23] The BOOST study data also supports this finding. As hypoglycemia is of particular concern in the elderly, the results of this post hoc analysis are reassuring. The low rates of hypoglycemia are suggest that there is no need

Table 2. Change in Study Parameters During the Follow-up Period

	IGlar U100 Cohort (n = 120)			IDegAsp Cohort (n = 89)		
	Baseline, Mean ± SEM	Follow-up Mean ± SEM	P	Baseline, Mean ± SEM	Follow-up Mean ± SEM	P
Body weight (kg)	69.65 ± 2.13	69.58 ± 2.13	0.714	68.51 ± 11.88	69.04 ± 1.19	0.873
BMI (kg/m^2)	26.78 ± 3.22	27.05 ± 0.69	0.830	26.97 ± 2.19	27.19 ± 3.42	0.812
SBP (mmHg)	132.22 ± 2.21	130.61 ± 1.59	0.736	130.65 ± 2.28	130.44 ± 1.64	0.907
DBP (mmHg)	80.56 ± 1.31	81.36 ± 1.07	0.782	78.97 ± 1.73	77.21 ± 1.71	0.901
FPG (mg/dL)	230.69 ± 7.49	154.78 ± 7.59	<0.001	236.08 ± 86.31	134.31 ± 51.40	<0.001
PPG (mg/dL)	295.18 ± 11.75	236.37 ± 10.58	<0.001	309.06 ± 106.76	180.76 ± 55.09	<0.001
HbA1c (%)	9.61 ± 0.78	8.56 ± 0.18	<0.001	9.61 ± 2.12	8.02 ± 1.02	<0.001
Serum creatinine (mg/dL)	0.95 ± 0.03	0.99 ± 0.03	0.901	1.01 ± 0.33	1.03 ± 0.39	0.897
Insulin dose (IU)	13.44 ± 0.41	24.1 ± 1.45	<0.001	10.23 ± 1.41	16.31 ± 3.78	0.768
Insulin dose/kg body wt. (IU), Mean ± SEM	0.20 ± 0.18	0.42 ± 0.57	<0.001	0.14 ± 0.09	0.23 ± 0.22	0.010

SEM = Standard error mean; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; BMI = Body mass index; FPG = Fasting plasma glucose; PPG = Postprandial plasma glucose; HbA1c = Glycated hemoglobin.

P < 0.05 considered as statistically significant, p computed by paired *t*-test.

Table 3. Percentage Reduction in Study Variables

	IGlar U100	IDegAsp	P (ANCOVA)
Percent change in body weight, Mean ± SEM	-0.11 ± 0.02	0.72 ± 0.66	0.102
Percent change in BMI, Mean ± SEM	-0.93 ± 0.08	0.85 ± 0.52	0.712
Percent change in FPG, Mean ± SEM	-33.04 ± 8.61	-34.63 ± 9.12*	0.041
Percent change in PPG, Mean ± SEM	-20.34 ± 2.89	-41.53 ± 4.76*	0.036
Percent change in HbA1c, Mean ± SEM	-9.88 ± 2.22	-16.55 ± 4.07*	0.044

SEM = Standard error mean; BMI = Body mass index; FPG = Fasting plasma glucose; PPG = Postprandial plasma glucose; HbA1c = Glycated hemoglobin.

P < 0.05 considered as statistically significant, p computed by ANCOVA test adjusted for baseline values.

for special precautions when using IDegAsp in the elderly.[13] A different approach was selected by Monnier and co-authors[24] to estimate the relative contribution of FPG and PPG to the overall glycemia. It was stated that PPG plays a major role in patients suffering from mild or moderate hyperglycemia. In Asian T2DM patients, PPG at 4 and 24 hours after meals was a predominant contributor to excess hyperglycemia in well-controlled patients and was equally important as FPG or PPG in moderately to poorly controlled patients with mean HbA1c up to 10%.[25] The data on the Indian population from this study indicates that PPG strongly correlates with HbA1c or contributes significantly to overall glycemic control. Hence, PPG monitoring will be more conducive for optimal glycemic control and prevent long-term diabetes complications than FPG alone in the absence of HbA1c, especially in developing countries.

The STARCH study on the Indian population showed that T2DM patients from across India consume higher carbohydrates (CHO) in their diet (such as rice, idli and so on), more than the dietary recommendations.[14,25] Around 64.1 ± 8.3% (95% confidence interval [CI] 63.27-64.93) of total calories came from total CHO in the T2DM group. This reflects that CHO consumption by Indian T2DM patients is higher (Δ4.1% above the upper limit of 60%) than that recommended by the guidelines and within the recommended limits as per the WHO

expert consensus. In addition to dietary and lifestyle modifications, multiple therapeutic strategies like insulin may benefit T2DM patients. This approach may have a leading role in an Indian setting where the role of α-glucosidase inhibitors (AGIs) is more significant because of CHO-rich meal, as seen in this study.[14] The choice of insulin for initiation has been a matter of debate, with evidence slightly being in favor of basal insulin as recommended by various western guidelines. Nonetheless, insulin initiation was considered at HbA1c levels as high as 8.5 or 9%, where the contribution of FPG was found to be substantially higher in the western population. On the contrary, a study done by Wang et al has conclusively revealed contribution of PPG at all quintiles of HbA1c in the South-East Asian population.[25]

While premixed analogs were a part of the International Diabetes Federation (IDF) guidelines to initiate insulin, studies revealed greater reduction of HbA1c at the cost of increased hypoglycemia. Availability of IDegAsp with data of reduced overall and nocturnal hypoglycemia versus premixed analogs as well as IGlar U100 made us ponder about its utility as a choice of once daily insulin in OAD failure subjects. IDegAsp demonstrated greater reduction in FPG, PPG and HbA1c as compared to IGlar U100. On the safety front, no statistically significant difference in hypoglycemia was noted between the two arms.

Conclusion

In conclusion, IDegAsp OD was significantly better as compared to IGlar U100 in improving glycemic control and in controlling PPG excursions without compromising FPG control or safety in Indian patients. IDegAsp OD provides predictable and efficacious FPG and PPG control in insulin-naïve patients with T2DM in a single injection while significantly reducing the risk of nocturnal-confirmed hypoglycemia compared with IGlar U100 in the Indian population. In the context of high CHO utilization in India, or patients with dominant postprandial hyperglycemia, premix insulin/co-formulation can offer effective and convenient glycemic control.

Key Messages

IDegAsp OD superiorly improves glycemic control and PPG excursions without compromising FPG control than IGlar U100. IDegAsp provides effective FPG and PPG control along with significant risk reduction of nocturnal-confirmed hypoglycemia. In a high carbohydrate consumption setting or predominant postprandial hyperglycemia, premix insulin/co-formulation can offer effective and convenient glycemic control.

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REVIEW ARTICLE

Association of Fructose Enriched Foods with Metabolic Syndrome and Cardiovascular Diseases

ANITA SHARMA*, KANUPRIYA VASHISHTH†, YASH PAUL SHARMA‡, GAURAV GUPTA#, DEVENDRA KUMAR SINGH¶

*Consultant Anesthesiologist
Grecian Hospital, Mohali, Punjab
†Research Scholar
‡Professor
Dept. of Cardiology
Post Graduate Institute of Medical Education and Research, Chandigarh, Punjab
#Head of Department
¶Senior Resident (Anesthesiologist)
Dept. of Anesthesiology and Critical Care Medicine
Grecian Hospital, Mohali, Punjab

A B S T R A C T

Cardiovascular diseases (CVDs) are the major causes of mortality and morbidity worldwide as well as in the Indian subcontinent, causing more than 25% of deaths. It has been predicted that these diseases will increase rapidly in India, making it a host to more than half the cases of heart disease in the world within the next 15 years. The World Health Organization (WHO) reports that in the year 2005 CVDs caused 17.5 million (30%) of the 58 million deaths that occurred worldwide. In the recent times, the association of metabolic syndrome (MS) is strongly linked with CVDs. MS is defined as a constellation of metabolic disorders in an individual. The main components of MS are dyslipidemia (higher triglyceride, low-density lipoproteins [LDL] and low high-density lipoproteins [HDL]), elevated blood pressure (BP), dysregulated glucose homeostasis, abdominal obesity and insulin resistance. Being one of the most widespread diseases in the world, almost half of the population of specific age groups in developed countries is affected by it. Studies have shown that the independent risk factors associated with MS increase the likelihood of CVDs. It has been postulated that excess intake of fructose promotes cell dysfunction, inflammation, intra-abdominal (visceral) adiposity, atherogenic dyslipidemia, weight gain, insulin resistance, hypertension thereby aggravating the chances for developing MS, type 2 diabetes and coronary heart disease.

Keywords: Cardiovascular diseases, metabolic syndrome, dyslipidemia, abdominal obesity, fructose, insulin resistance

Introduction

As the engines of health transition gather pace, the epidemic of cardiovascular diseases (CVDs) is accelerating globally, advancing across regions and social classes. CVDs, one of the noncommunicable diseases have become the major public health problem in developed and developing countries. Globally CVD deaths represent about 30% of all deaths. As per the World Health Organization (WHO) reports, it is predicted that almost 23.6 million people will die from CVDs, mainly from heart disease and stroke by 2030, both becoming the single leading cause of death. Different studies are throwing light on the diseases associated with increased CVD risk such as metabolic syndrome (MS) as with lifestyle changes new and

Address for correspondence
Dr Gaurav Gupta
Head of Department
Dept. of Anesthesiology and Critical Care Medicine
Grecian Super Speciality Hospital, SAS Nagar,
Mohali - 160 062, Punjab
E-mail: drgauravgupta433@gmail.com

more complex disease conditions have emerged. The new millennium is witnessing the emergence of a modern epidemic, i.e., MS, with frightful consequences to the health of humans worldwide and its associated comorbid conditions. Studies have shown that MS patients possess a significantly greater risk for the development of CVD in general and coronary artery disease (CAD) in particular, studies have even reported a positive correlation between MS and carotid atherosclerosis.

The etiology of CVD in patients with MS may involve: coronary atherosclerotic disease, arterial hypertension, left ventricular (LV) hypertrophy, diastolic dysfunction, endothelial dysfunction, coronary microvascular disease and autonomic dysfunction.

The pathogenesis of CVD in the MS is multifactorial as it can be caused by one or more factors associated with this condition such as the systemic abnormalities, insulin resistance, diabetes and/or inflammation. It is seen that each component of MS independently affects cardiac structure and function, but their combination under this syndrome seems to carry additional risk.

MS is a complex disease bearing a high socioeconomic cost and being considered as a major epidemic worldwide. Although many definitions and classifications of MS are available two definitions in the widespread are used globally; one proposed by the WHO and other by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (Table 1).

Broadly MS is defined as concurrence of overweight, abdominal fat distribution, dyslipidemia, disturbed glucose and insulin metabolism and hypertension (Fig. 1), historically the concept of MS dates back to 1988 when Reaven for the first time had put forward the concept of syndrome X, which was later named as MetS. However in 1999, WHO introduced the term 'metabolic syndrome' to include the cluster of factors as a clinical entity. Recent studies have also added other abnormalities such as chronic pro-inflammatory, hyperuricemia, prothrombogenic states, nonalcoholic fatty liver disease (NAFLD) and sleep apnea to the entity of this syndrome making its definition even more complex. Along with being a risk factor for CVDs, MS even predisposes an individual

Table 1. Consensus Definitions from Different Associations on Metabolic Syndrome

National Cholesterol Education Program-Adult Treatment Panel III, 2001	American Heart Association/ National Heart, Lung and Blood Institute Scientific Statement, 2005	International Diabetes Federation, 2006	Harmonizing the Metabolic Syndrome, 2009
Three or more of the following:	Measure (any 3 of 5 constitute diagnosis of metabolic syndrome)	Central obesity as defined by ethnic/racial, specific WC and two of the following:	Three or more of the following:
WC >102 cm for men, >88 cm for women	WC >102 cm in men, >88 cm in women	Triglycerides ≥150 mg/dL	Central obesity as defined by ethnic/racial, Specific WC
Triglycerides ≥150 mg/dL	Triglycerides ≥150 mg/dL or on drug treatment for elevated triglycerides	HDL-chol <40 mg/dL for men; <50 mg/dL for women	Triglycerides ≥150 mg/dL or on drug treatment for elevated triglycerides
HDL-chol <40 mg/dL in men; <50 mg/dL in women	HDL-chol <40 mg/dL in men; <50 mg/dL in women or on drug treatment for reduced HDL-chol	BP ≥130/85 mmHg	HDL-chol <40 mg/dL in men; <50 mg/dL in women or on drug treatment for reduced HDL-chol
BP ≥130/85 mmHg	BP ≥130/85 mmHg or on antihypertensive drug treatment in a patient with a history of hypertension	FPG ≥100 mg/dL	BP ≥130/85 mmHg or antihypertensive drug treatment
FPG ≥110 mg/dL	FPG ≥100 mg/dL or on drug treatment for elevated glucose		FPG ≥100 mg/dL or on drug treatment for elevated glucose

WHR = Waist-to-hip ratio; WC = Waist circumference; BP = Blood pressure; FPG = Fasting plasma glucose; Chol = Cholesterol.

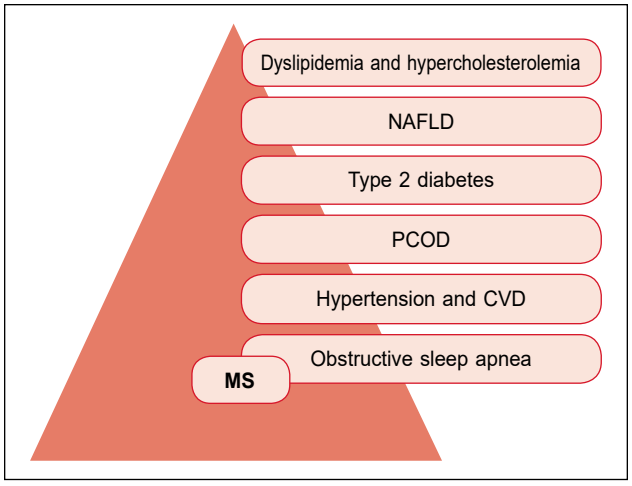

Figure 1. Metabolic syndrome and its associated disorders.

to a greater risk for developing type 2 diabetes. Changes in human behavior, high energy fast food environment, sedentary lifestyle, have recently been attributed to be associated with progression towards MS.

In the present world, there has been an augmented understanding of MS and its associated diseases followed by a subsequent increase in clinical attention directed towards its prevention, due to its strong association with premature morbidity and mortality. Numerous studies have reached to the consensus now that insulin resistance and obesity are main determining factors involved in the common pathologic mechanism of the MS and its associated comorbid conditions. Evidences have suggested that the progression towards MS begins early in life and with persistence from childhood to adolescent/ adult life results in type 2 diabetes, CVDs and other associated diseases.

The symptoms of MS develop over a predisposed background thought to be established at a young age and are not necessarily manifestations of age, recent trends in modern diets, habits, lifestyle changes likely influencing health and behavior in increasingly younger populations makes up for a dangerous predisposition.

Pathophysiology of Metabolic Syndrome and CVD Progression

Understanding the pathophysiology responsible for MS will prove to be a beneficial aid for best treatment options. While the exact mechanisms responsible for increased CVD risk have not been elucidated, studies have thrown light on insulin's action and the role of

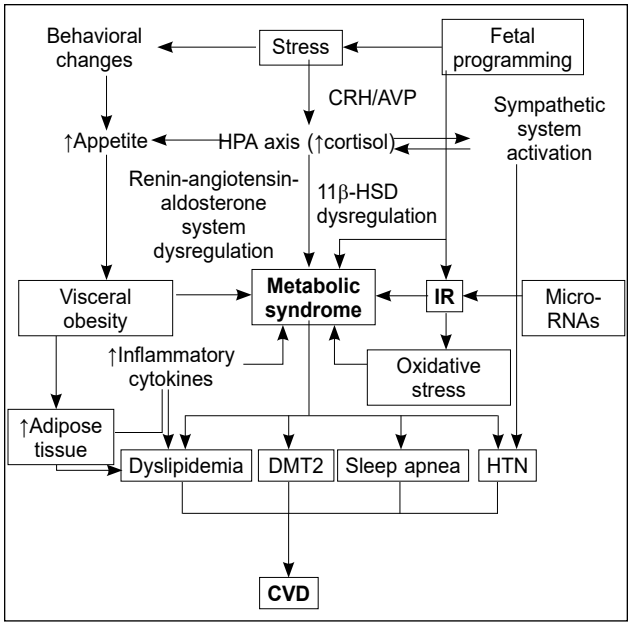

Figure 2. Metabolic syndrome and CVD progression.

obesity and its associated pathological mechanisms (Fig. 2). The excess adiposity associated with MS plays an important role towards the progression of MS associated CVD. Obesity especially abdomino-visceral, is associated with certain pathogenic factors that contribute to normal glucose homeostasis: high plasma levels of free-fatty acids (FFAs), increased hepatic glycogenesis and peripheral insulin resistance. It is seen that in obesity, cytokines mediated release of inflammatory molecules such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, plasminogen activator inhibitor (PAI), C-reactive protein and resist in occurs from adipose tissues and immune cells due to the initiation of a chronic inflammatory state via cytokines. The link between obesity and inflammation stems from the fact that pro-inflammatory cytokines are over expressed in obesity, this inflammatory process acts as a homeostatic mechanism to prevent the accumulation of excess fat. It is established that the starting signal for inflammation in obesity is overfeeding and the pathway origins in all metabolic cells e.g., in adipocyte, hepatocyte or myocyte.

Clinical and non-clinical studies have shown that consumption of nutrients may acutely evoke inflammatory responses, furthermore metabolic cells such as adipocytes respond to this insult by beginning inflammatory response. It is seen that lipid storage and weight increase requires an anabolic process while inflammation stimulates catabolism including lipolysis, as a result due to chronic lipolysis FFAs are liberated continuously and are further transferred via portal vein

to liver. Studies have shown that increased plasma FFAs along with inflammatory cytokines trigger a response that results in decreased insulin sensitivity in tissues that depend on insulin which is caused by inhibition of receptor signaling, this situation is also referred to as insulin resistance (IR) further leading to increased insulin synthesis and secretion by β pancreatic cells and resulting in compensatory hyperinsulinemia, following it FFAs are oxidized simultaneously in the liver, triggering neoglucogenesis and thus increasing glycemia. Concomitantly, there is an increase in the synthesis of very low-density lipoproteins (VLDLs) that further generate small, dense atherogenic LDLs.

Studies have shown an extensive role of TNF-α in the systemic inflammatory response triggered by obesity, it is seen that within adipose tissue macrophages account for maximum TNF-α production and it has also been seen that TNF-α expression levels are higher in obese patients, a link between increased levels of circulating TNF-α levels and IR has been established. The pathway of IR via TNF-α occurs through serine phosphorylation (inactivation) of both the insulin receptor and insulin receptor substrate-1 (IRS-1), as a result a diminished activation of phosphoinositide 3-kinase (PI3K) occurs which is a main governing molecule of insulin's metabolic effects. One of the mechanisms by which TNF-α is thought to trigger IR is via activation of nuclear factor-κB (NF-κB) signaling, which further results in activation of inflammatory cascade. Another mechanism by which TNF-α is thought to contribute to IR is through the elevated levels of circulating FFAs caused by induction of lipolysis and stimulation of hepatic lipolysis; however, this mechanism has only preliminary supporting evidence and extensive studies are needed to completely validate the findings.

Studies have depicted that insulin's action also plays a crucial role towards CVD progression in MS patients. Deedwania in his study; noted that insulin's action can lead to hypertension via stimulation of vascular smooth muscle cell hypertrophy; in addition, insulin could also cause hypertriglyceridemia and high-density lipoprotein (HDL) cholesterol through increased catecholamines. It is also reported that insulin can lead to secretion of prothrombogenic PAI-1.

Studies have shown that hyperinsulinemia may even lead to increased sensitivity to angiotensin II, which further could result in increases in cell growth, PAI-1, intracellular adhesion molecule-1, etc. Defects in insulin sensitivity may interfere with insulin-stimulated vasodilation. IR is also associated with endothelial dysfunction, which is characterized by impaired endothelium-dependent vasodilation, reduced arterial compliance and accelerated process of atherosclerosis. Along with obesity and IR, studies have even thrown light on the role of matrix metalloproteinase (MMPs) in MS and associated CVDs. Progression towards MS associated CVD begins via alterations of the arterial vasculature, which begins with endothelial dysfunction and lead to micro- and macrovascular complications. It is seen that remodeling of the endothelial basal membrane that promotes erosion and thrombosis occurs due to multifactorial pathogenesis that includes leukocyte activation, increased oxidative stress and also an altered MMP. Being endopeptidases, the primary role of MMPs is to degrade matrix proteins, such as collagen, gelatins, fibronectin and lamin, and can be secreted by several cells within vascular wall. The activity of MMPs is regulated by tissue inhibitors of MMP (TIMPs) and also by other molecules, such as plasmin. The role of MMPs in plaque instability causing serious vascular complications has been reported in several studies. It has been demonstrated that an impaired MMP or TIMP expression is associated with higher risk of all-cause mortality.

In the recent years, MMPs have garnered considerable interest due of their association with many disease conditions. It is seen that different components of the MS provide an impetus for MMP synthesis and even their activity; these include hypertension, dyslipidemia, hyperglycemia, pro-inflammatory and pro-oxidant markers, on the other hand, anti-inflammatory cytokines like adiponectin are inversely associated with MMPs. Extensive studies have come up to the conclusion that among the several MMPs collagenases (MMP-1 and MMP-8) and gelatinases (MMP-2 and MMP-9) are strongly associated with MS progression and its associated diseases, even few studies targeting MMPs in patients coronary diseases and diabetes and have shown fruitful results. In the near future, targeting MMPs and their activators can prove beneficial in treating and understanding the MS complexity and its associated diseases.

Nutritional Factors Influencing Metabolic Syndrome

In the recent times, a trend towards the shift in the energy balance accompanied by sedentary lifestyle and increased caloric intake is gathering considerable importance, and is being attributed to technological advances and improved economic status in Western countries and even developing countries. Studies have shown that the Westernization of diets, along with high calorie foods is certainly becoming an important

contributor to MS epidemic, and the increased incidence of the MS now even threatens developing countries.

In the past, physicians and scientists have made an association between dietary energy from fat and body fat, following which a large market is being popularized and promoted for low fat diets, interestingly however, the decline in dietary fat consumption has not corresponded to a decrease in obesity in fact, an opposite trend has emerged. It is seen that diets high in saturated fats induce weight gain, IR and hyperlipidemia in humans and animals. Despite putting effortless emphasis on fat reductions no significant benefits relative to the obesity epidemic have emerged, increasing evidence now suggests that the rise in consumption of carbohydrates, particularly refined sugars high in fructose, appears to be at least one very important contributing factor. Recent epidemiological and biochemical studies clearly suggest that high-fructose intake may play an important role in progression towards MS.

At present, the market is flooded with large quantities of popular, convenient, prepackaged foods, soft drinks and juice beverages containing sucrose or high-fructose corn syrup. Fructose, which is found naturally in many fruits, is now consumed by humans in large quantities in the commonly available popular foods. Studies have shown that an approximate 25% increase in per capita fructose consumption over the past 30 years clearly co-exists, which increase in the prevalence of obesity and MS; high-fructose diets have been shown to induce IR, weight gain, hyperlipidemia and hypertension in several animal models including rats, hamsters and dogs.

In human studies, fructose consumption is seen to be associated with the development of hepatic and adipose tissue IR and dyslipidemia due to its ability to induce hepatic *de novo* lipogenesis (Fig. 3). Different biomechanical studies have suggested that sugar consumption causes adverse effects because of rapid hepatic metabolism of fructose which is catalyzed by fructokinase C, which further results in increased uric acid levels and even generates substrate for *de novo* lipogenesis.

Studies have shown glucose transporter 5 (GLUT5) present at the brush border and basolateral membranes of the jejunum aids in the absorption of fructose from the intestine into the portal blood; as a result massive fructose uptake by the liver occurs via this route. It is noted that the hepatic metabolisms of both glucose and fructose are different; fructose is phosphorylated by fructokinase, forming fructose-1-phosphate, which can then be converted to several three-carbon molecules, including glyceraldehyde, dihydroxyacetone phosphate and glyceraldehyde 3-phosphate. It is seen that some of these three-carbon molecules via the process of gluconeogenesis could be converted to glucose, or could also be used to generate other products such as triglycerides (TGs), which further can be packaged into VLDL by the liver. As VLDLs travel through the bloodstream, TGs can be hydrolyzed by lipoprotein lipase to form nonesterified fatty acids (NEFAs) and monoacylglycerol, which are further taken up by adipose tissue and resynthesize to TGs, therefore excessive fructose consumption can lead to high levels of FFAs and obesity. It is already stated that the role of the adipose tissue is to take up FFAs and store it in the form of TGs, however in obesity it is seen that this storage capacity reaches to its maximum resulting in an impaired ability of adipose tissue to acquire dietary fatty acids, as a result increased levels of fatty acids occurs in circulation.

Studies have shown that signaling abnormalities in adipocytes can also trigger lipolysis of TG stores resulting in efflux of fatty acids into the bloodstream thereby augmenting the problem. Few studies have thrown light that high levels of NEFAs in the bloodstream have a positive correlation between obesity, IR, type 2 diabetes and metabolic dyslipidemia, these NEFAs are eventually taken up ectopically by nonadipose tissues such as the liver and skeletal muscle, where they may be stored as TG or diacylglycerol and interfere with metabolic pathways such as the response to insulin, contributing to IR and MS. Numerous studies have shown that the build-up of lipids in the liver and other tissues in obesity contributes to an increased mitochondrial oxidation of fatty acids, further generating peroxidation products that stimulates IκB kinase (IKK)β and, therefore, NF-κB activation. Various studies have even found a correlation between fatty acid or lipid treatment and NF-κB activation. Under

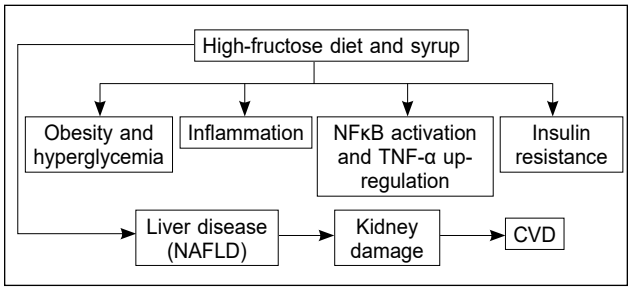

Figure 3. High-fructose consumption and its associated effects.

basal conditions NF-κB is found in the cytosol bound to its inhibitor, IkB, but upon activation of IKKβ, which phosphorylates IkB and marks it for degradation, NF-κB is allowed to enter the nucleus, where it induces transcription of specific genes.

The proteins encoded by these genes include pro-inflammatory cytokines such as PAI-1, TNF-α, IL-6 and IL-1β; however, the mechanisms responsible for IKKβ and NF-κB activation in obesity are unclear. TNF-α being a mediator of inflammation and immune response is a versatile cytokine that alters tissue remodeling, epithelial cell barrier permeability, activation of macrophages and recruitment of inflammatory filtrates different downstream signaling cascades activated by TNF-α have been elucidated. TNF-α, by binding to various receptors such as TNFR1 results in the activation of various transcription factors e.g., NF-κB as well as intrinsic and extrinsic apoptotic cascades mediated by caspase-8 and cytochrome C.

Recent studies have shown the involvement of TNF-α in mitochondrial membrane destabilization, resulting in formation of pathological pores causing mitochondrial permeability transition thereby activating the intrinsic pathway of apoptosis mediated by cytochrome C in many diseases. Numerous nonclinical studies have delineated the effect of fructose and its associated activated pathological pathways on the progression towards MS associated CVDs in rodents. In a study, Shiu et al delineated the apoptotic and antisurvival effects on rats hearts when administered high fructose diet (HFD). It was seen that rats on HFD besides having elevated levels of all MS markers, had abnormal myocardial architecture, enlarged interstitial space and increased cardiac apoptotic cells. The role of intrinsic and extrinsic apoptotic markers such as Fas-dependent apoptotic proteins (TNF-α, TNFR1, Fas ligand, Fas receptor, FADD, activated caspase-8 and activated caspase-3), mitochondria dependent apoptotic proteins (Bax, Bak, Bax/Bcl-2, Bak/Bcl-xL, cytosolic cytochrome C, activated caspase-9 and activated caspase-3) was delineated in the study. Rats on HFD had up-regulated levels of the above stated markers. Further cardiac insulin-like growth factor 1 (IGF-1-related survival proteins (IGF-1, IGF-1R, p-PI3K and p-Akt) and Bcl-2 family associated pro-survival proteins (Bcl-2 and Bcl-xL) were down-regulated in rats on HFD.

Parks et al and Katan et al, showed in their short-term studies that diets rich in carbohydrates, particularly sugars (sucrose, fructose) resulted in increase in serum triacylglycerol concentrations and decreased HDL concentration, therefore indicating a risk towards developing CVD. Few studies have also thrown light on the involvement of various oxidative stress markers (nicotinamide adenine dinucleotide phosphate or NADPH) and pro-inflammatory cytokines (IL-1, IL-6) and hypothesize a possible role of NF-κB and TNF-α in the progression of MS thereby leading to CVDs. Numerous studies have found that dietary composition of carbohydrate can result in development of left ventricular hypertrophy and cardiac pathology. It is believed that with increased concentrations of fructose diets the trend towards CVD risk will markedly rise in near future.

Conclusion

With rising financial implications and with a concomitant impact on human health, MS in the recent past has gathered considerable concern; its presence is an important risk factor for the development of CVDs and type 2 diabetes. At present, the key principles involved in the management of patients with MS are early identification of patients, effective treatment regular follow-up, pharmacological therapy and lifestyle modifications. In the current scenario, the mechanisms that contribute to MS associated diseases remain unclear, extensive research is underway that might help in understanding the pathological pathways and novel treatment options. The most important contributory factors which have emerged as the important links in MS are sedentary lifestyle, altered dietary requirements and obesity.

The consumption of fructose has increased, largely because of an increased consumption of soft drinks and many juice beverages containing sucrose or high-fructose corn syrup. Dietary high-fructose intake has been suggested to be an important factor contributing to the development of symptoms of MS. Recent evidence suggests that fructose feeding in rats develops the features of the MS model in many of the same pathophysiological deficits as noted in MS in humans, such as IR, dyslipidemia, hyperinsulinemia, hypertricylglycerolemia, impaired glucose tolerance, increased uric acid levels, hypertension, myocardial functional abnormalities and heart failure. If not alarmed and the different economies do not make necessary interventions to the growing MS epidemic, individuals from all age groups will be severely affected limiting their full overall development and progression.

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REVIEW ARTICLE

Transition Care in Type 1 Diabetes. Five Questions and Five Principles

SIMRITA CHAWLA*, JUBBIN JAGAN JACOB†

*Transitional Coordinator, Dept. of Endocrinology, Christian Medical College and Hospital, Ludhiana, Punjab
†Professor and Head, Dept. of Endocrinology, Christian Medical College and Hospital, Ludhiana, Punjab

ABSTRACT

Management of type 1 diabetes mellitus during the period of adolescence to young adulthood is among the most challenging in the field of diabetes care. At around the age of 18 there is a physical transfer of care from pediatric physicians to adult physicians. Alongside there is transfer of responsibility of self-care from parents to the patient over a period of time. Unique medical problems encountered in this age group include puberty induced increase in insulin requirements, an increase in psychiatric comorbidities including substance use and abuse, disconnect with health care teams, and problems related to reproductive care and contraception. This is reflected in the poorer outcomes seen in this age group including an increase in acute complications, increase in hospitalizations with diabetic emergencies, poor glucose control and an increase in loss to follow. The poor metabolic control during this period leads to establishment of early chronic macro and microvascular complications. A structured transition care is a planned purposeful process that address these unique medical, psychological, and vocational needs among these patients that smoothens out the process of transfer to adult care teams. The models that have been proven to be useful in improving outcomes include the use of separate transition clinics, use of transition coordinators and enrollment into young patients support groups. Regardless of the model used there are five overarching principles that define this process of transition care. They can be summarized in five Cs which include: appropriate communication, assessment of self-care needs, building competence, using collaborative teams, and finally providing care and counseling for psychological issues.

Keywords: Transition care, type 1 diabetes mellitus, adolescence, young adults, transfer of cares

Introduction

Diabetes management in our country is a challenging task regardless of the type of diabetes mellitus or associated comorbidities and complications. Among the many complicated patients that are encountered in a diabetic clinic the most challenging in our opinion is the management of type 1 diabetes mellitus (T1DM) during adolescence and early young adulthood. During this period young patients may encounter a transfer of care from a pediatric endocrinologist to an adult endocrinologist and a transfer of responsibility of day-to-day diabetes care from parents to self (Fig. 1). Additionally, some children may also encounter the need to adjust to a new living situation away from the support of family and friends in a new city as they leave for college, further training, employment, or marriage. Transition of care is distinct from transfer of care among adolescents with T1DM in that it is defined as "a planned purposeful process that specifically addresses the unique medical, psychological, social, vocational and educational needs of these children as they move from pediatric to adult care for chronic lifelong diseases like T1DM" (Fig. 2).[1]

Address for correspondence
Prof. Jubbin Jagan Jacob
Dept. of Endocrinology,
Christian Medical College and Hospital,
Ludhiana, Punjab - 141008
E-mail: jubbin.jacob@gmail.com

Q1. Why is Transition Care Needed?

A child or an adolescent diagnosed with a chronic disorder like T1DM must carry the disease into his/her

adulthood and beyond. The primary goal of transition care is to help the child with T1DM to seamlessly shift from a pediatric family centred diabetes care environment to an independent adulthood (Fig. 3). There are several reasons why transition care is essential. These include:

- **Underdeveloped prefrontal cortex in young adults.** Though crossing the age of 18 is considered the threshold of adulthood in most countries it is slowly being realized that complete maturity of the prefrontal cortex only happens in the early twenties.[2] The prefrontal cortex is an area responsible for many of the important cognitive behaviors that are associated with adulthood (Fig. 4).
- **Insulin resistance related to pubertal hormone changes.** Puberty induces a combination of hormonal changes involving the gonadal and growth axis that leads to an increase in insulin resistance. Normal children in late puberty secrete almost double the amount of insulin compared to children in early puberty. In adolescents with T1DM this corresponds to an increased requirement of exogenous insulin and difficulty in achieving glucose targets. Additionally, puberty may unmask dawn phenomenon in many adolescents and girls may note an increase in insulin requirements in the premenstrual period.[3,4]
- **An increase in psychological issues during this period.** Almost all adolescents struggle during this period where they are developing their identity and autonomy independent of the family. Adolescents with T1DM have to face additional challenges including adhering to insulin and self-monitoring regimes, uncomfortable interactions with peers, classmates and colleagues at work, disagreements with family regarding diabetes self-care, fear of short-term complications like hypoglycemia and hospitalizations and fear of long-term complications and feelings of guilt when glucose control is suboptimal.[5] All these lead to an increase in the prevalence of anxiety disorders, panic attacks and psychological distress.[6] Depression and depressive symptoms are common among T1DM in this age group. In the SEARCH study girls with T1DM had a 10.9% prevalence of moderate to severe depressive symptoms.[7] Eating disorders are 2.4-fold more common among girls with T1DM compared to girls without diabetes of similar age.[8]
- **Sexual and reproductive health issues.** There is no reason for adolescents and young adults with T1DM to behave any differently from their peers without diabetes. All young patients should receive preconceptional counseling and be given appropriate contraception advice.

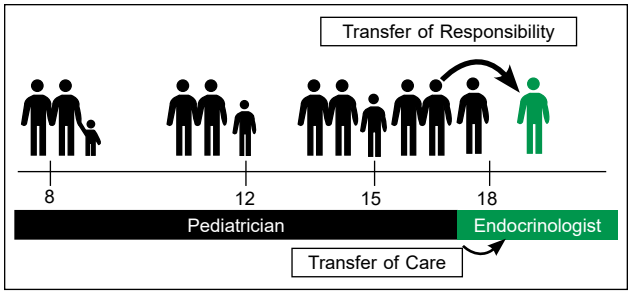

Figure 1. The concept of transfer of care at attaining adulthood among children with lifelong chronic diseases like type 1 diabetes mellitus who need long-term medical supervision and contact. There is also a gradual transfer of responsibility in the day-to-day management of the disease from the parent to the patient at some point during these years.

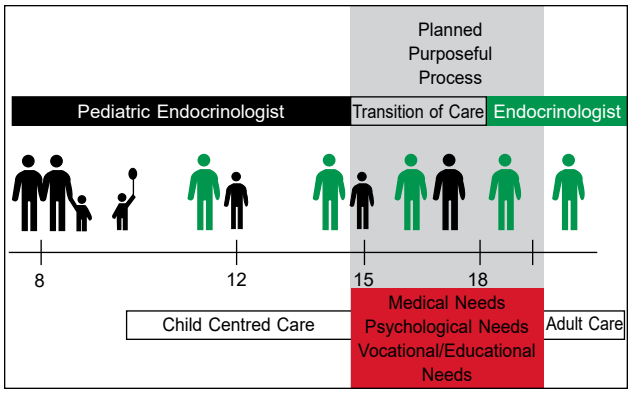

Figure 2. The concept of transition of care is explained as a planned, purposeful process that addresses the specific needs of the patient during this process of transfer of medical care and responsibilities at the attainment of adulthood. The process however starts much before the age of 18 and can continue for as long as it is required.

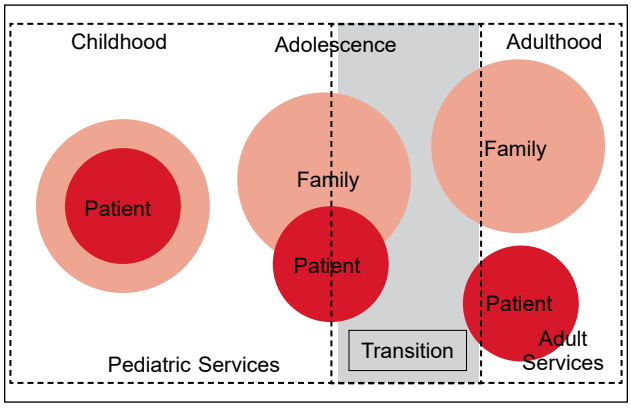

Figure 3. The differences between family and patient dynamics in childhood, adolescence, and adulthood and the placement of transition services.

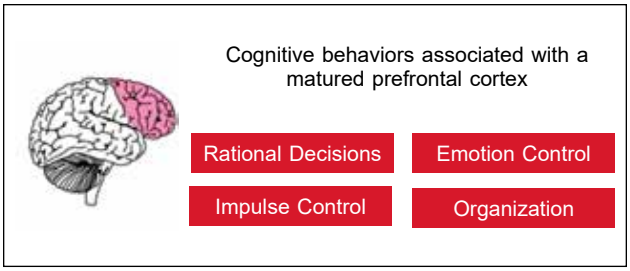

Figure 4. Important cognitive functions and behaviors associated with the prefrontal cortex that take longer than 18 years to attain full maturity.

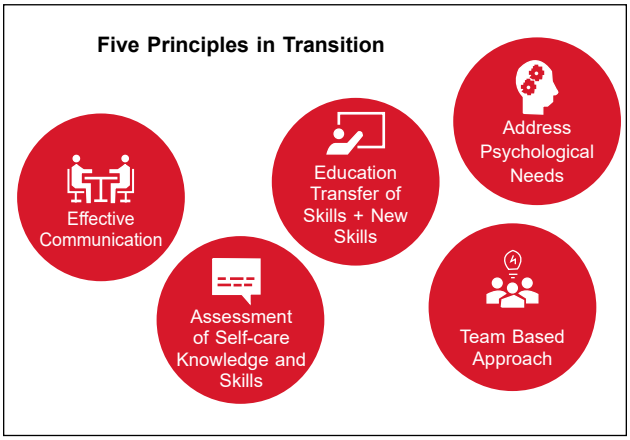

Figure 5. The five primary principles of transition care are summarized in the figure. They can be visualized as the five "Cs" for easy recall. This includes communication, care assessment, competence building, collaboration, and counseling/care for psychological issues.

- **Alcohol, smoking and drug use.** Again, there is no evidence that alcohol, tobacco, and drug use rates are any different among adolescents with T1DM compared to peers who do not have diabetes. Alcohol worsens hyperglycemia immediately and increases the risk for delayed hypoglycemia. All though abstaining from alcohol is the safest response, in practical terms, young people with T1DM need to be educated about safe drinking and decreasing any risks by maintaining hydration, eating adequate carbohydrates, reducing insulin doses if required, and monitoring blood glucose levels.
- **Social, educational, and vocational changes.** Adolescents during the transition period have major changes in their life that includes going for undergraduate or postgraduate studies on occasions to cities far from where they have been brought up in, independent living in hostels and other student accommodations with difficult access to appropriate diets and meals, earning for their livelihood, training and internship which may include shift and night duties and in a small number of cases getting married and starting a family of their own.

Q2. Are Bad Outcomes Noted in the Transition Period?

As noted above, the period of transition is potentially associated with the interruption of a long-term "comfortable" relationship with health care providers especially at a time when the adolescent is confronting multiple issues related to changing metabolism and the development of identity and autonomy. Poor health choices with smoking, alcohol use especially binge drinking, and loss of parental supervision of diet and insulin administration may complicate matters further. The poor outcomes noted during this period include:

- **Poor metabolic control.** Current hemoglobin A1c (HbA1c) targets from the American Diabetes Association (ADA) for children between the ages of 13 years and 18 years is <7.5% (58.5 mmol/moL) and after the age of 19 years is <7% (53 mmol/moL).[9] Most teenagers and young adults struggle to meet these targets. Data from the SEARCH Study in youth with T1DM suggests that only 32% of teenagers (13 to 18 years) and 18% of the young adults (19 onwards) achieved these targets.[10] This stands in contrast with 56% of adults achieving HbA1c targets of <7% (53 mmol/moL).[11]
- **Loss to follow-up.** Transitioning older teenagers and young women are at particularly high-risk of disengagement from health care providers because of the competing distractions. Though there is limited published information about the frequency of contact between young people and health care professionals. Clinic attendance was significantly lower (8.5 ± 2.3/years vs. 6.7 ± 3.2/years) over 3 years when teenagers were transitioned from pediatric to adult services in Germany when compared to previous attendance at pediatric clinics.[12]
- **Risk of acute complications.** A large cohort of 1,243 children (aged from infancy to 19 years) was followed up for 3,994 person-years in Denver. The primary outcome in the study was the rate of acute presentation to emergency department with ketoacidosis and severe hypoglycemia. The overall incidence of diabetic ketoacidosis was 8 episodes/100 person-years in the cohort. The highest incidence of diabetic ketoacidosis was seen among adolescent between the ages of 13 years and 19 years with rates over 12 episodes/100 person-

years.[13] Another study from Ontario looked at 1,507 patients with type 1 diabetes followed for 4 years after transition to adult clinic. The hospitalization rates increased from 7.6 episodes/100 patient-years prior to transition to 9.5 admissions/100 patient-years after transition ($p = 0.03$).[14]

- **Emergence of chronic complications of diabetes.** Chronic complications related to diabetes are extremely rare among preadolescents. Even among adolescents, clinically apparent diabetes related complications are very rare. Although preclinical evidence of diabetes related microvascular complications maybe present in adolescents. Evidence of early atherosclerotic processes including fatty streaks and intimal lesions are seen in autopsy studies conducted on adolescents and young adults.[15]
- **Premature mortality during transition.** Mortality rates are increased in patients with diabetes compared to the general population at all ages. Within this cohort of patients with diabetes mellitus, men have an increased risk of death compared to women at all age groups except between the ages of 5 years and 15 years. However, the relative risk (RR) of death is much higher in women at all ages. The RR of death (standardized mortality ratio [SMR]) is 4 for women and 2.7 for men. The peak SMR in women was between the ages of 20 years and 29 years at which point it was as high as 5.7. Most of this information has come from a very large cohort of patient with insulin treated diabetes from the United Kingdom.[16]

Q3. What Are the Current Transition Models That Have Been Shown to Work?

Currently, there are no randomized controlled trials examining the overall efficacy of a structured transition program among adolescents and young adults. However, structured transitional care has been demonstrated in cohort studies to have better outcomes in terms of less loss to follow-up, better HbA1c levels, fewer admissions with diabetic ketoacidosis, and fewer long-term complications at the end of the transition.[17,18] There are three basic models which can be followed which have been found to improve outcomes.

- **Dedicated transition or young adult clinics.** The earliest and simplest model appears to be a dedicated transition clinic staffed by both pediatric and adult diabetes teams which handle children in transition for a given period prior to complete transfer of care to the adult diabetes services. Logan et al. from the United Kingdom reported data from a structured intervention that consisted of a year-long transition clinic which comprised of both pediatric and adult physicians and nurses. Patients were seen three times a year and on two out of the three occasions, the patient could choose the provider they wished to see (doctor, nurse, dietician, or clinical psychologist). Over a period of 3 year, patients had an 84% attendance rate, a drop of HbA1c from 9.7% to 9.0% (first to last visit), and a significant increase in percentage of patients with HbA1c less than 7.5%.[19]
- **Transition coordinators.** A second more economical approach rather than having a full-fledged transition clinic is to have a separate transition coordinator. The first use of transitional care coordinators was documented from Australia. The coordinators helped to maintain attendance at the dedicated young adult clinic.[20] A similar Maestro project in Canada used a systems navigator or "maestro" to help access adult medical care as stand-alone in routine pediatric to adult transition patients. Additionally, the intervention consisted of a website, a regular newsletter, group meetings, and access to especially devised young adult educational events. The program was successful in reducing loss to follow-up and helping older transition patients reconnect with medical care.[21]
- **Young adult support group.** Everyone needs a friend in their life, and it is more convenient to communicate with the one who is passing through the same condition as you are. So, forming a young adult group where all these young adults can discuss their issues or even come up with new solutions is yet another way to ease out the transition period. A recent publication has highlighted the utility of support groups for young adults with type 1 diabetes during the transition period. In this study, the participants attended monthly support groups sessions for 5 months. Eighty percent of the participants attended at least three sessions and two-thirds of patients had significant improvements in HbA1c at the end of the program.[22]

Q4. What is the Ludhiana Model of Transition Care?

At Christian Medical College and Hospital, Ludhiana we use a model that utilizes both a transitional care coordinator and a young adult support group. Children are encouraged to enroll into transition between the ages of 15-16 years and continue to be in the transition

group till they are comfortable with our checklist of care/education goals. The transitional coordinator volunteers her time in addition to her primary job as a research associate and helps keep the costs of the care model low. The support group primarily communicates with each other on a WhatsApp group which is moderated by the transitional coordinator. Enrollment into the group is after an informed consent. All transitioning adolescents and young adults have access to a psychologist, but payments must be made if her services are utilized.

Q5. What Are the Primary Principles of Transition?

Regardless of which model is chosen for transition there are some overarching principles that need to be considered when planning out a transition care model. The five principles are summarized in Figure 5. The five Cs of transition are mentioned below:

- **Communication.** You need to communicate with the child. To be a favorable communicator you need to adapt the model of active listening where you understand and respond without invalidating the child's point of view. Ask them about their thoughts on the disease and make them realize the importance of managing it.
- **Care (self-knowledge) assessment.** This includes a thorough assessment of the child's knowledge about diabetes and skills required to manage diabetes on a day-to-day basis. It is usually that the family is accountable for the child's health care prior to adolescence. You can assess their skills through tools like questionnaires in which you can ask about their knowledge about insulin, insulin self-administration, insulin dose adjustments, insulin storage and disposal of sharps. Additionally, skills at self-monitoring, diabetes management if they get sick etc. should be assessed and skills that very likely are available in the family need to be now transferred to the child.
- **Competence building.** Once self-care knowledge is assessed a plan should be made to transfer this knowledge and skills from the family/health care provider to the child. This may include skills like insulin administration, self-monitoring of glucose and dose adjustments to more complicated skills like making doctor's appointments, getting medications in time, and having emergency contacts. New skills that need to be provided during transition include safe driving with diabetes, handling stress at work/schools/examinations, handling peer pressure, safe drinking, and contraceptive advice.
- **Cooperation and collaboration.** The fourth most important principle of transition is realizing that successful transition needs teamwork of health care professionals, family members and friends. Health care teams could include physicians, diabetes specialist nurses, dieticians, psychologists, podiatrists, and transition coordinators.
- **Counseling and caring for psychological issues.** As previously mentioned the period of transition is associated with a variety of psychological issues. Many of these require specialized care and appropriate therapy. Transition teams should be able to make this available to children who require this.

Transition period is a vulnerable time for emerging young adults with chronic medical conditions. As adolescents start moving to a different place to gear up for their independent earning, they lose contact with their health care providers which leads to gaps in medical care. There is a large overlap of psychosocial issues so a team-based approach of primary care and psychology would be beneficial. Transition checklists in the clinics can help to address the problems young adults are facing and can ease up the transition process. Awareness and early initiation with a well-structured process for transition is essential.

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CONTEMPORARY ARTICLE

Motivating Persons Living with Diabetes for Insulin/Injectable Therapy

SANJAY KALRA*, NAVNEET AGRAWAL†, ABHINAV GARG‡

*Dept. of Endocrinology, Bharti Hospital, Karnal, Haryana, India;
University Center for Research & Development, Chandigarh University, Mohali, Punjab, India
†Dept. of Diabetology, Diabetes Obesity Thyroid Centre, Gwalior, Madhya Pradesh, India
‡Dept. of Medicine, Medicutis Clinic, Prashant Vihar, New Delhi, India

A B S T R A C T

Motivating patients to initiate or intensify insulin is a challenging aspect of diabetes practice. This paper reviews certain motivational strategies and methods used for insulin initiation/intensification. It places various domains of motivational interviewing in perspective, under a single umbrella, making it easier for practitioners to understand the art and science of insulin motivation.

Keywords: Diabetes, insulin therapy, patient-centered care, person-centered care, psychosocial aspects

Introduction

A large proportion of patients with diabetes is poorly controlled, and suffers an unnecessary burden of poor glycemic control before their therapy is up-titrated or intensified.[1] While many reasons have been put forward for this clinical inertia, one of the major reasons is physician's inability (or their self-perceived inability) to motivate patients to initiate or intensify insulin therapy.[2]

The model we share in this article is being used with success at our centers. It is a simple and easily replicable method, which can be learnt by physicians and paramedical staff alike, and used in resource-limited or time-challenged settings as well as in optimal health care environments.

Address for correspondence
Dr Sanjay Kalra
Dept. of Endocrinology, Bharti Hospital, Karnal, Haryana, India; University Center for Research & Development, Chandigarh University, Mohali, Punjab, India
E-mail: brideknl@gmail.com

Insulin Motivation – 'WATER' Approach

The WATER approach[3] is a mnemonic coined for a method of motivational interviewing (MI) used at our centers. It is a checklist designed to remind the health care practitioner about the basics of MI, and to ensure good quality provider – patient bonding so that optimal therapeutic outcomes are achieved (Box 1).

Box 1. The WATER Approach

W – **Welcome warmly**	• Body language • The OPD encounter
A – **Ask and assess**	• Identifying and using cues • Internal, external, laboratory • Hierarchy of questioning • The insulin encounter
T – **Tell truthfully**	• Mid-Sentence analysis • Verbal/Nonverbal cues • Analogy building
E – **Explain with empathy**	• Examples/Experience– sharing • Demonstration • Coping skills training
R – **Reassure and return**	• Agree upon the next visit/contact • End with positivity

W stands for 'Welcome warmly', which reminds the health care provider (HCP) to greet the patient, with genuine warmth, in a gender, age- and socio-culturally appropriate manner.

Body Language

The physician should make a conscious effort to learn the nuances of body or nonverbal language, make the patient feel at ease, diagnose his or her level of comfort, and plan further conversation or therapeutic intervention. A pleasant greeting is followed by a detailed history taking, reflected by A for Ask and Assess. The patient is asked for his or her perception of diabetes. History is accompanied by an assessment of barriers to insulin therapy, cues[4] (such as concerns, symptoms, signs, laboratory reports and external influences), which may stimulate insulin use and felt needs of the patient.

Hierarchy of Questioning

Using the correct order of questioning is of utmost importance in history taking, if one wants to motivate a major change in health-related behavior, e.g., insulin use. While conversing, one should slowly move from the patient's comfort zone to his or her non-comfort zone, from non-personal to personal, from familiar to unfamiliar. One should first identify and/or create a major felt need, and then position insulin as the treatment for that need, while focusing on its positive benefits.

A conversation where the doctor asks about sexual function or financial issues before talking of weight loss or asthenia will be not welcomed by most patients.

Cues

The motivation model utilizes 'internal' and 'external' cues, gleaned from an intensive history taking, and 'laboratory' cues, taken from investigation reports, for insulin motivation. Internal cues are signs and symptoms, which have a high index of perceived severity, or are a 'felt need' for the patient, such as a frozen shoulder, recurrent urogenital infection or weight loss. External cues may be motivation by 'social' or 'environmental' factors. An impending or developing renal failure due to diabetes, or a child learning about the complications of diabetes at school, may act as a factor for insulin acceptance. Laboratory results such as a high HbA1c or a high vibration perception threshold on biothesiometry can be utilized for insulin motivation.

Mid-Sentence Analysis

During the process of "asking and assessing", one can keep a close watch on the patient's verbal language or nonverbal cues, to assess the patient attitudes towards insulin. For example, one can start a sentence as "Guidelines tell us to begin insulin in you ……" and wait to see the patient's response. If he or she moves backwards or says "But I will never take insulin!" or makes a wry face, the sentence can be completed as "……. but let us try tablets for 2 weeks. Do you mind taking an expensive tablet with only 2 years history of experience?"

If on the other hand, the patient keeps a neutral stance and facies, one can complete the conversation as: "…, so let us begin twice daily insulin."

Such a mid-sentence analysis is an effective tool of reducing "counseling casualties" and getting resistant patients to gradually accept insulin or other appropriate therapy.

One should T (Tell the truth) to the patient after having assessed his needs. The truth or HCPs clinical opinion should be told in an appropriate manner, described as the five-pointed CARES approach (Box 2). These are the five attributes, which a diabetes care professional must possess.[5]

Telling the truth alone is not enough; one should Explain the situation with empathy. Explanation is accompanied by analogy building,[6] quotation of examples and use of demonstration devices. Cues gleaned during history are utilized to provide a starting point for patient engagement, and given back to patients, paraphrased as suggestions or solutions.

The last step is R (Reassure and Return). Reassurance is essential to ensure that the patient returns for follow-up.

The physician may not succeed in motivating the patient for insulin or injectable therapy during the first OPD encounter, but will at least shift him or her from the pre-contemplation to the contemplation phase (Prochaska's theory of knowledge).[7]

Box 2. The CARES Approach

Confident Competence
Authentic Accessibility
Reciprocal Respect
Expressive Empathy
Straightforward Simplicity

Experience – Sharing with Peers

Most oriental cultures encourage sharing of illness-related experiences with friends and community. Health is usually not reviewed as a private matter, unlike in western cultures. Depending upon social mores, one can use examples of successful insulin initiators in the community to encourage insulin initiation and intensification.

Coping Skills Training

Reassurance is combined with coping skills training (CST), which helps the patient handle the stress of diabetes in a better manner.

Coping skills training is a method of improving the method(s) by which a person responds to a seemingly insurmountable challenge (for example, living with diabetes, controlling diabetes). Each and every person has both positive and negative coping skills. Our model of diabetes counseling focuses on diagnosing a particular patient's coping methods. One should begin by Asking and assessing the individual's current coping styles. This gives an idea of the negative skills which have to be Eliminated, before positive coping mechanisms can be Introduced and Internalized. These changes have to be Observed on a Ongoing basis, so that one can continually Upgrade one's Understanding and health care-related behavior. This has been termed the AEIOU approach.[8] Table 1 lists the common coping styles that can be identified and optimized.

Table 1. Coping Styles

Negative	• Blaming oneself, e.g., I have developed diabetes because of sins in my past life • Blaming others, e.g., my sister didn't take care of me so I developed high blood pressure • Extremely bad thoughts, e.g., I will die due to high glucose • Pervasive bad thoughts 24 x 7, e.g., Thinking only and only about diabetes throughout the day
Neutral	• Acceptance, e.g., I accept that diabetes and insulin are a part of my life
Positive	• Put in perspective, e.g., Let me count my blessings and strengths • Positive spin-off, e.g., Insulin will make me more disciplined in my life • Pleasant thoughts, e.g., May be I will make new friends at the next diabetes advocacy meeting • Plan for the future, e.g., Let me begin saving money to buy an insulin pump

Reducing Discomfort of Change

One should always strive to reduce the discomfort associated with change.[9] Simple steps such as building a rapport with the patients, abbreviating bad news, and expanding good news, making change appear as if it were a choice, handing overcharge to the patient, and breaking the change into small bits, help in reducing the discomfort associated with change of lifestyle or pharmaceutical modality.

Conclusion

This article tries to encapsulate, under one umbrella, the various facets of patient motivation for insulin or injectable therapy in people with diabetes. It should sensitize physicians and other diabetes care professionals to the science behind the art of insulin motivation, and help improve the quality of care provided to persons living with diabetes, by reducing clinical inertia as well as patient resistance related to insulin usage.

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CASE REPORT

Cocktail Inferno – Multiple Sclerosis with Type 2 Diabetes Mellitus in a Patient with Lepromatous Leprosy

SONIA JAIN*, PRIYANKA DATE†, NEERAJ DODKE‡

*Professor
†Senior Resident
Dept. of Skin and VD
‡Senior Resident
Dept. of Medicine, Mahatma Gandhi Institute of Medical Sciences (MGIMS), Sewagram, Maharashtra

A B S T R A C T

Co-occurrence of multiple sclerosis with type 2 diabetes mellitus with lepromatous leprosy is rare. We hereby report a case of multiple sclerosis with type 2 diabetes mellitus with lepromatous leprosy in a middle-aged female. She was clinically diagnosed as having multiple sclerosis with type 2 diabetes mellitus and presented with fever, ENL and neuritis. Her MRI reports were normal but she had a positive slit-skin smear and skin biopsy as lepromatous leprosy. Proceeding with this diagnosis, she was treated with baclofen for spastic bladder, antibiotics for urinary tract infection, oral hypoglycemic agents and oral steroids with multibacillary treatment for leprosy with type 2 reactions. She responded well and currently is being followed-up.

Keywords: Multiple sclerosis, leprosy, diabetes mellitus, demyelinating neuropathy

Introduction

Multiple sclerosis is a disorder with heterogeneous clinical and pathologic features reflecting various pathways to tissue injury.[1] Inflammation, demyelination and axonal degeneration are the key pathologic mechanisms, which lead to clinical manifestations.[2,3] However, the cause of multiple sclerosis remains unknown.[4,5] The most widely accepted theory suggests that it begins as an inflammatory immune-mediated disorder characterized by autoreactive lymphocytes.[1,6] Later, the disease is dominated by microglial activation and chronic neurodegeneration.[2]

Leprosy (Hansen's disease) is an infectious disease caused by *Mycobacterium leprae* that involves the skin and peripheral nerves. Early diagnosis and a full course of treatment are critical for preventing lifelong neuropathy and disability.[7] Although the infection is highly responsive to treatment, leprosy became an important global health concern due to deformities and disabilities of the eyes, hands and feet secondary to neuropathy which are often irreversible and require lifelong care and rehabilitation. Therefore, early diagnosis and management are necessary to minimize the likelihood of these disabilities.[8]

Type 2 diabetes mellitus is characterized by hyperglycemia, insulin resistance and relative impairment in insulin secretion. It is a common disorder with a prevalence that rises markedly with increasing degrees of obesity.[9]

The prevalence of type 2 diabetes has risen alarmingly in the past decade,[10] in large part linked to the trends in obesity and sedentary lifestyle.[11]

Case Report

A 55-year-old female was brought by her relatives to the skin department. She had flexor spasms, difficulty in walking, spastic bladder with an indwelling catheter since last 4 years and was diagnosed to have multiple sclerosis. She had multiple admissions for fever and urinary tract infection and was on oral hypoglycemic

Address for correspondence
Dr Sonia Jain
Professor
Dept. of Skin and VD
MGIMS, Sewagram, Maharashtra
E-mail: soniapjain@rediffmail.com

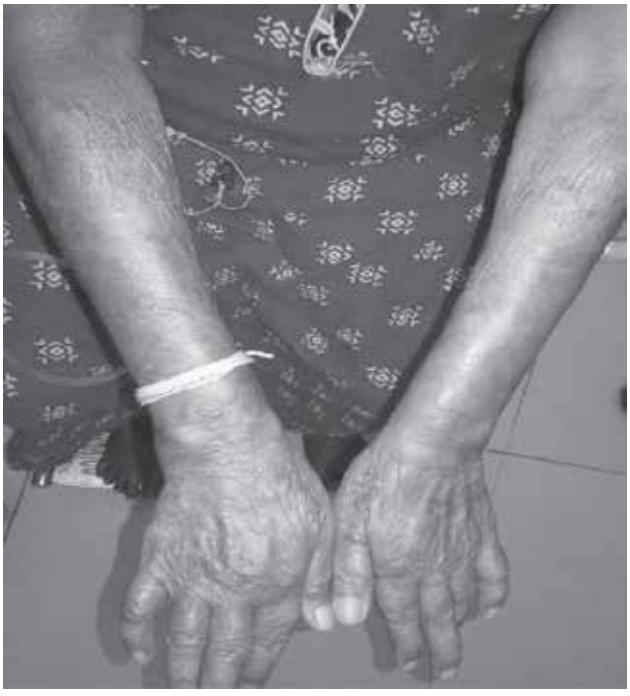

Figure 1. Multiple red-colored raised lesions (ENL) over body.

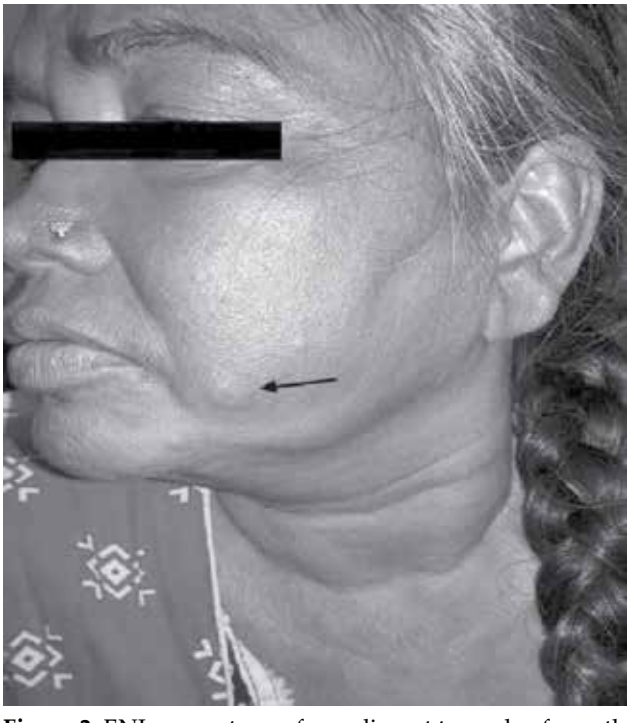

Figure 2. ENL present over face adjacent to angle of mouth (*arrow*).

agents on regular basis. She presented with fever, multiple red-colored raised lesions (Erythema nodosum leprosum or ENL) all over the body (Fig. 1), with weakness, tingling and numbness over both upper and lower limbs. ENL were also present over her face

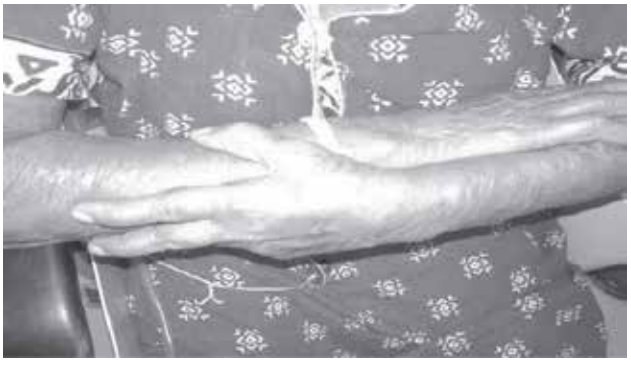

Figure 3. Xerosis and ichthyosis visible over bilateral upper limbs.

adjacent to the angle of mouth (Fig. 2). Xerosis and ichthyosis characteristic of leprosy was visible over bilateral upper limbs (Fig. 3). There was no history of photosensitivity or any drug intake or application of any local irritant prior to the initial lesion.

Her detailed central nervous system evaluation revealed upper motor neuron type of paraparesis, sensorimotor with proximal as well as distal muscle involvement with urge incontinence suggestive of spastic type of neurogenic bladder. Her mental functions were intact with no cranial nerve involvement. Cardiovascular system, respiratory system and per abdominal evaluation was within normal limits.

Her routine blood biochemistry was normal except for low hemoglobin levels (5.9%), raised white blood cell (WBC) counts (15,800) and raised random blood sugar (RBS) levels (157 mg/dL). Urine analysis revealed urinary tract infection for which she was treated with antibiotics. Bladder care was given. She was treated with baclofen. Skin examination revealed positive slit-skin smear for acid-fast bacilli with bacteriological index of 3.5 and skin biopsy consistent with lepromatous leprosy. She was put on oral steroids for type 2 lepra reaction and multibacillary anti-leprosy treatment for leprosy. Appropriate oral hypoglycemic agents were continued as she was reluctant with insulin administration. Brain imaging was normal. She responded well and her flexor spasms decreased. A psychiatric consultation was sought for her depression due to chronic illness and was started on antidepressants.

Discussion

Dominant or recessive genetic mutations give rise to a number of inherited neuropathies. The basic pathology happens to be in the Schwann cells, the myelinating unit of the neuron leading to defective myelination,

alteration of the axonal cytoskeleton and disruption of the axonal transport.[12] Genes involved in the axonal transport are the chief site of mutation in the majority of inherited neuropathies leading to the atrophy of the axons and directly correlate with the clinical features in the inherited neuropathies.[12] Diabetes mellitus is characterized by a number of sensorimotor and mixed neuropathies. The pathologic hallmark of neuropathies occurring in long-term diabetics involves the advanced glycation end products, persistent oxidative stress, polyol pathway flux and protein kinase C activation, ultimately contributing to microvascular disease and nerve dysfunction.[13]

Common symptoms of multiple sclerosis include sensory abnormalities including pain, motor symptoms due to involvement of the pyramidal tracts, visual disturbances, ataxia and Lhermitte sign. The pattern of abnormalities can vary from subtle limb weakness or sensory symptoms like Uhthoff phenomenon to more severe sensorimotor noncompressive myelopathies like acute transverse myelitis. Retrobulbar neuritis and optic neuritis have been the common causes of transient visual disturbances in multiple sclerosis. The onset is often polysymptomatic. Neuropathy is an early feature in Hansen's disease, as earliest diagnostic lesions are characterized by hypoesthesia.[14] Though early sensory loss is a common finding in leprosy, in some cases, patients can present with pain, which is often late in the course of the disease.[15,16]

In the tuberculoid spectrum of the Ridley-Jopling classification, neuropathy occurs in the proximity of the skin lesions, as against neuropathy in lepromatous disease, which is more generalized. Common nerves include the ulnar, median nerves (claw hand), the common peroneal nerve (foot drop), the posterior tibial nerve (claw toes and plantar insensitivity), the facial nerve (lagophthalmos), the radial cutaneous nerve, and the great auricular nerve. Subclinical neuropathy is found more commonly, as against it was previously believed in leprosy. These results may have implications for the design of ErbB2 RTK-based therapies for both leprosy nerve damage and other demyelinating neurodegenerative diseases.[17]

Here we report this case as to the best of our knowledge, leprosy with multiple sclerosis has not been reported in literature.

Conclusion

Multiple sclerosis, Hansen's disease and diabetes mellitus are multisystem diseases with distinct etiologies affecting the sensory as well as motor nerve fibers. It is considerably rare to find a demyelinating, infectious and autoimmune disease of the nerves to coexist in the same patient. All these conditions can be managed simultaneously and successfully.

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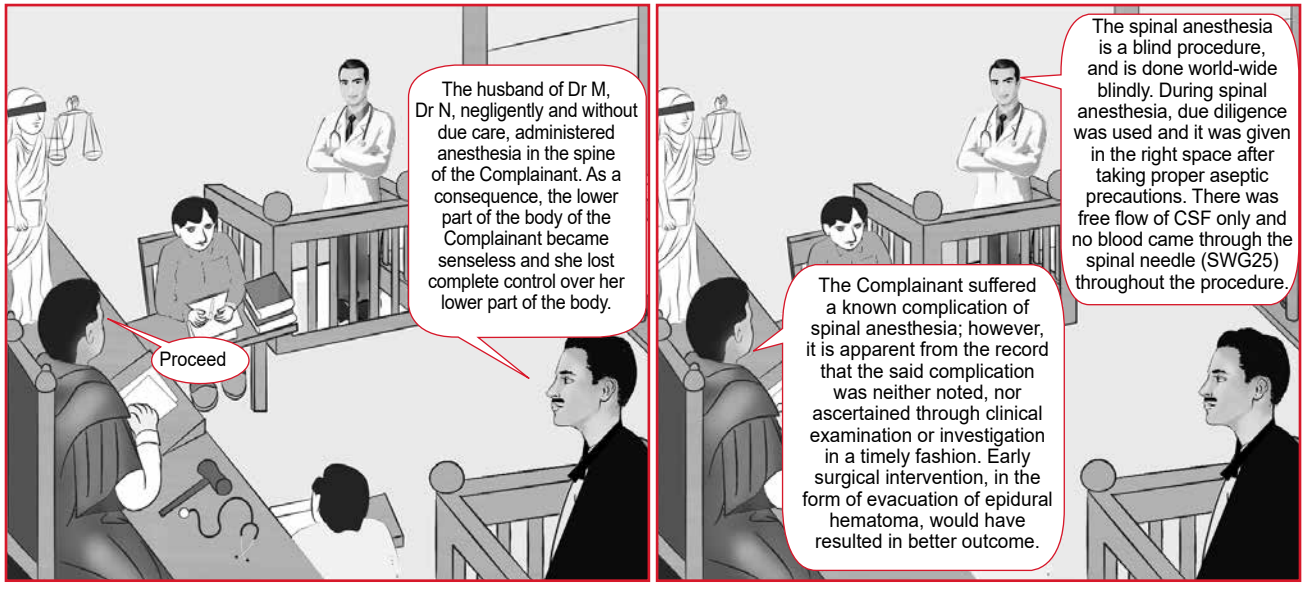
Failure to Timely Diagnose and Intervene in a Known Complication of a Procedure



Lesson: The Disciplinary Committee of the Delhi Medical Council (DMC) found that the Respondents failed to exercise reasonable degree of skill, knowledge and care, in the treatment administered to the Complainant, which was expected of an ordinary prudent doctor and recommended that names of the Respondents be removed from the State Medical Register of the DMC for a period of 15 days.

Course of Events

28.11.2008: The Complainant was admitted for delivery in Nursing Home A under Dr M, as she had been under her care during prenatal period. The Complainant was rushed into the operation theater on 28th November, 2008 in hurry by creating panic situation stating that the baby had passed stools.

Allegations of Complainant

In the operation theater, the husband of Dr M, Dr N, who is posted in a Government Hospital, negligently and without due care, administered anesthesia in the spine of the Complainant. As a consequence, the lower part of the body of the Complainant became senseless and she lost complete control over her lower part of the body.

The baby was delivered but the Complainant could not recover from the ailment caused to her on account of professional negligence on the part of Dr M and Dr N.

The Complainant was constrained to consult various experts to get herself examined and magnetic resonance imaging (MRI) report clearly shows that the anesthesia was wrongly administered leading to the said ailment, which completely immobilized the Complainant and she has been confined to bed for almost 2½ years. It was further alleged by the Complainant that Dr N is employed with Government Hospital and has been carrying out the private practice in unauthorized and illegal manner. The Respondents did not render any medical help to the Complainant after she developed the above said problem on account of negligence on the part of the Respondents.

The Respondents did not disclose/inform the Complainant or her relatives regarding the nature of the ailment, which afflicted the Complainant after administration of said anesthesia. The Respondents have neglected the Complainant and willfully committed an act of negligence, which has led to immobilization of the Complainant.

Rejoinder of Respondents

Dr M, the Respondent stated that an absolute emergency and life-threatening condition for the Complainant had developed as the membranes had ruptured spontaneously and fetus had passed the stool (meconium) inside. There was immediate threat to the baby aspirating the meconium-stained liquor in mouth and lungs, which could have been fatal for the baby.

The anesthetist on the call was contacted telephonically and since he was busy in another operation and would be available after approximately 2 hours, another anesthetist was contacted but his mobile did not connect after repeated attempts.

It was only after failure to contact the anesthetist despite repeated attempts that Dr N was contacted in this emergency situation. On being apprised of the emergency situation and the danger to the baby, Dr N agreed with great reluctance only on moral and humanitarian grounds in the best interest of both, the Complainant and her to be born baby.

Dr N, the Respondent stated that the spinal anesthesia was given after taking due care and attention. During spinal anesthesia, due diligence was used and it was given in the right space after taking proper aseptic precautions. There was free flow of cerebrospinal fluid (CSF) only and no blood came through the spinal needle (SWG25) throughout the procedure. As for the loss of control over the lower part of the body is concerned, it is an unfortunate and an isolated incident for which they cannot be blamed.

The Respondents arranged for the urgent and immediate MRI themselves, as soon as they noticed the complication. The MRI scan showed epidural hematoma and spina bifida. The spina bifida is a congenital anatomical defect about which the Complainant did not tell them. The presence of such defect in the spine cannot be ascertained beforehand, before giving spinal anesthesia especially in pregnant women or before starting surgery. They cannot be blamed for such congenital defect in the spine.

MRI report also does not mention about any neurological damage committed during the anesthesia procedure. The epidural hematoma in the MRI scan could not be due to the abnormal arterial venous plexus/ arteriovenous malformations present in the epidural space. The spinal anesthesia is a blind procedure, and is done world-wide blindly.

Observations of DMC

The spinal anesthesia is a blind procedure. The Complainant suffered a known complication of spinal anesthesia; however, it is apparent from the record that the said complication was neither noted, nor ascertained through clinical examination or investigation in a timely fashion. The Complainant was administered spinal anesthesia for purposes of delivery on 28th November, 2008. Postoperatively, the Complainant lost complete control over her lower part of the body and complained of acute pain in the spinal region which was attributed to normal pain associated with the procedure and was managed by administering injection voveran, a painkiller.

As per literature, maximum chances of recovery in epidural hematoma (post spinal anesthesia) are within first 8 to 10 hours of injury, a time period which had already elapsed prior to her neurological consultation. It was only on 29th November, 2008 in the morning that the spinal complication was noted and neurological consultation was sought.

The treating team failed to assess the gravity of the clinical condition of the Complainant. When the Complainant was diagnosed as having neurological deficit on 29th morning, it would have been desirable to get an urgent MRI, which would have assisted in confirming the diagnosis and prompted an early surgical intervention in the form of evacuation of epidural hematoma, which would have resulted in better outcome.

As regards, the conduct of Dr N of indulging in private practice, in spite of being in Government service needs to be looked into by the Government.

Order of DMC

In light of the observation made hereinabove, it was the decision of the Disciplinary Committee that the treating team of Dr M and Dr N failed to exercise reasonable degree of skill, knowledge and care in the treatment administered to the Complainant, which was expected of an ordinary prudent doctor. The Disciplinary Committee, therefore, recommended that names of Dr M and Dr N be removed from the State Medical Register of the DMC for a period of 15 days.

Reference

1. DMC/DC/F.14/Comp.881/2013/ Dated 23rd July, 2014.

■■■■

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