

# Obesity, Family History of Diabetes, and Consanguineous Marriages are Risk Factors among Urban Population in South Indian City of Bengaluru

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In 2017, approximately 424.9 million adults (age 20-79 yrs) were affected by diabetes, with 4 million deaths. Global diabetes burden is estimated to increase up to 628.9 million people. Moreover, diabetes care costed approximately \$727 billion in 2017. In addition to mortality and economic cost, diabetes exerts huge effect on a patient's life. It affects the adults at their most productive years which may lead to less productivity, mobility, and considerable expenditure. Diabetes has become one of the leading causes of mortality and morbidity in India as well. According to international reports, over 73 million adults were affected with diabetes in India in 2017. The total economic burden was estimated at around \$32 billion. Of note, India will be home to the world's largest population with diabetes by 2045 with approximately 134.3 million patients suffering from type 2 diabetes mellitus (T2DM). Approximately, 1 million are attributable to diabetes. India also houses the second largest population of T2DM patients with undiagnosed disease at around 42.2 million. Furthermore, India also reports more 16,000 cases of type 1 diabetes every year in children and adolescents with 128,500 children and adolescents suffering from type 1 disease in 2017. India also have the third largest population of elderly with T2DM of about 11 million patients. Diabetes is also responsible for loss of billions of dollars in GDP in India as well as worldwide [1].

With the increasing number of diabetes patients in India, it is necessary to diagnose the disease at an early stage for early intervention and reduced risk of subsequent complications. Diabetes is a multifactorial and heterogenous disease owing to several genetic and

environmental factors. Over the decades, several risk factors have been identified for development of T2DM in adults. Obesity and family history of diabetes are two of the major risk factors for onset of the disease in adults. In addition, several systematic studies have revealed that parental consanguinity may also a risk factor for developing T2DM. Thus, individual with obesity, family history of diabetes, and parental consanguinity should be screened to diagnose T2DM. As detection of disease at early stage may lead to better prognosis.

To this end, we have studied these risk factors in urban population in South Indian city of Bengaluru [2]. In a retrospective data analysis, we analysed data of 519 patients who attended the diabetic out-patient clinic. Patients provided the aetiological data through a questionnaire during their routine clinic visit. Obesity, family history (maternal history of T2DM) and parental consanguinity were found to be important risk factors for early onset of T2DM.

Obesity is increasing at an alarming rate worldwide. In the United States, more than two-thirds of the adult population is overweight or obese. In India, 180 million adults and 14 million children are obese. It has been doubled in children and tripled in adults from 1980 to 2015. Obesity affect medical, psychological, and social condition of the individuals and may lead to type 2 diabetes in adults. T2DM and obesity are linked with insulin resistance. Non-esterified fatty acids, glycerol, hormones, cytokines, proinflammatory substances, and other substances are in obese individuals which leads to insulin resistance. In

addition, insulin sensitivity and the modulation of  $\beta$ -cell function decreases in the condition of obesity. In diabetes,  $\beta$ -cell dysfunction reduces insulin secretion resulting in increase in fasting blood glucose and postprandial blood glucose. Thus, insulin resistance along with impairment of  $\beta$ -cell function leads to the development of diabetes in obese individuals. We also found that obesity was a major risk factor for T2DM which is in line with previous studies. Our results showed that the proportion of patients with T2DM being obese or overweight patients was eight times higher than patients who were non-obese/non-overweight.

High-fat diet and physical inactivity may be responsible for obesity apart from genetic traits. However, in this study, we observed that obesity was comparable between patients with active or strenuous lifestyle and sedentary group of patients. Thus, nutritional transition, to highly saturated fats, sugar, and refined foods and the transport facilities and increased stress, particularly in the urban populations may play an important role in increasing obesity. Of note, several systematic studies have shown that obesity management leads to delay in progression to T2DM from pre-diabetes [3]. Weight loss in obese patients with T2DM also improve glycemic control and reduce the need for glucose-lowering medications. American Diabetes Association (ADA) recommended following for weight management in diabetic patients:

1. Diet, physical activity, and behavioural therapy to achieve 5% weight loss for overweight and obese patients with type 2 diabetes.
2. Such interventions should be high intensity and focus on diet, physical activity, and behavioral strategies to achieve a 500-750 kcal/day energy deficit.
3. Diets that provide the same caloric restriction but differ in protein, carbohydrate, and fat content are equally effective in achieving weight loss.
4. For patients who achieve short-term weight loss goals, long-term comprehensive weight maintenance programs should be prescribed. Such programs should provide at least monthly contact and encourage ongoing monitoring of body weight (weekly or more frequently), continued consumption of a reduced calorie diet, and participation in high levels of physical activity (200-300 min/week).
5. To achieve weight loss of >5%, short-term (3-month) high-intensity lifestyle interventions that use very low-calorie diets ( $\leq 800$  kcal/day) and total meal replacements may be prescribed for carefully selected patients by trained practitioners in medical care settings with close medical monitoring. To maintain weight loss, such programs must incorporate long-term comprehensive weight maintenance counselling.

6. Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents who are overweight (BMI  $\geq 85$ th percentile) or obese (BMI  $\geq 95$ th percentile) and who have one or more additional risk factors for diabetes.

World Health Organization (WHO) and American Diabetes Association (ADA) considered family history of diabetes as the most important risk factor for diabetes. They are 2-6 times more likely to develop T2DM compared to patients without family history of diabetes. It has been long observed that non-diabetic male with family history of diabetes has elevated levels of fasting plasma glucose compared to males without family history of diabetes. Moreover, in Asian adolescents with both diabetic parents, higher FPG was observed compared to adolescents with only one diabetic parent. Hence, first degree relatives of diabetics are at high risk of having prediabetes and eventually develop diabetes. However, it is important to distinct "Diabetes family history" and "genetic risk" as both are not the same. Both genetic and environmental factors which mostly remain same in terms of cultural and behavioural aspects such as shared environment, shared behaviours, and epigenetic effects are represented by family history. Of note, energy metabolism and cardiovascular risk associated with family history and sedentary behaviours contribute to the development of prediabetes and diabetes in patients with family history of diabetes. It is important to note that individuals with family history of diabetes have more knowledge about symptoms of diabetes and more aware of organs affected by diabetes compared to individuals without family history of diabetes [4]. However, other studies have reported otherwise. Family history of diabetes is also associated with other metabolic abnormalities. In this study, more than half of the patients diagnosed with T2DM had positive family history of diabetes. Interestingly, the risk was greater with maternal than paternal family history of T2DM. Same has been reported elsewhere as well [5]. Subgroup analysis revealed that the proportion of patients diagnosed with T2DM in the younger age group ( $\leq 40$  years -50 yrs) was two times than the older patient group ( $>50$  yrs) ( $p < 0.0001$ ). Patients with new onset or recent ( $< 3$  months) onset of diabetes in the one year study period (July 2016-2017), the proportion of patients with young onset diabetes [YOD (aged  $\leq 40$  years)] was numerically the highest compared to other age groups and significantly higher in patients in the age groups  $< 40$ -50 years compared to patients in the age group of  $> 50$  years. Patients with family history of T2DM were twice at higher risk of YOD than patients who did not have family history of T2DM. Thus, individuals with family history of T2DM should be screened for early diagnosis of T2DM. If patients with prediabetes are diagnosed early, lifestyle modification

may delay onset of the disease. Moreover, early detection of diabetes will improve patients' outcome and possibility of complications, if managed well.

Consanguineous marriages have been attributed for development of numerous disorders which has genetic risk factor. Marriage between first cousins are the most common among consanguineous marriages. Along with other cultural and environmental factors, consanguineous marriages have also been found to be a risk factor for developing diabetes. Parental consanguinity has been found to be a modifier of effect of family history of diabetes on impaired fasting glucose [6]. It has also been found to be a risk factor for developing impaired fasting glucose in populations with higher number of consanguineous marriages [7]. In this study, we observed that the parental consanguinity was a significant risk factor for developing early onset diabetes (age  $\leq$  40 years) after adjusting for obesity as a risk factor. However, consanguinity was not a significant independent risk factor in non-obese patients. Thus, such individuals also should be screened for prediabetes and diabetes as recommended.

In summary, our results are in line with previous studies suggesting that obesity, family history of diabetes, and consanguineous marriages are risk factors for developing diabetes in South Indian city of Bengaluru. Regular screening as recommended by standard professional guidelines should be performed of such individuals with high risk.

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