

# Problems of Diabetes Therapy in Women: From Menstruation, Infertility, and Menopause

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## INTRODUCTION

The challenges of managing diabetes during adolescence are manifold. During adolescence and emerging adulthood, females undergo significant cognitive, emotional, and developmental changes. With the beginning of puberty, changes in insulin sensitivity related to growth and sexual maturation require close monitoring of blood glucose levels and necessary adjustments to insulin therapy in type 1 diabetes mellitus (T1DM) patients. Though majority of T1DM adolescents are treated with intensive insulin regimens (either with multiple daily injections or continuous subcutaneous insulin infusions) to achieve an American Diabetes Association (ADA) recommended glycated haemoglobin (HbA1C) goal <7.5%,<sup>1</sup> glycemic targets should be based on a risk-benefit assessment, preferably individualized, keeping in mind the adverse neurocognitive effects of hypoglycemia as well as diabetic ketoacidosis and chronic hyperglycemia. Adherence to modified nutrition therapy may be challenging in adolescents who exhibit disordered eating behaviors and depression, sometimes even with omission of insulin for weight control predisposing them to dangerous

metabolic events. Psychosocial distress among emerging adults may pose additional difficulties like non adherence to therapy, leading to suboptimal glycaemic control with increased risk of acute and chronic diabetic complications. It is prudent to take on board mental health professionals, parents, teachers and day care personnel to improve adherence and metabolic outcomes. The importance of diabetes self-management education and support (DSMES) cannot be emphasized enough either. At puberty, preconception counselling emphasizing on the risks of malformations associated with unplanned pregnancies and poor glycemic control, should be incorporated into routine diabetes care.<sup>1</sup>

Unlike adults, type 2 diabetes mellitus (T2DM) among adolescents, exhibits a rapid decline in pancreatic beta cell function with early onset of complications.<sup>2,3</sup> Female sex, family history of diabetes, adiposity, and low socioeconomic status are additional risk factors in youth with T2DM.<sup>3</sup> Over the past two decades, a rising trend of T1DM diagnosis among overweight (BMI>85<sup>th</sup> %) and obese (BMI>95<sup>th</sup> %) youths has become apparent. These obese individuals with evidence of insulin

resistance may also exhibit islet cell autoimmunity with auto-antibodies against pancreatic beta cells, and has been considered as suffering from “double diabetes.” In youths genetically susceptible to T1DM, obesity aggressively contributes to pancreatic autoimmunity and beta cell destruction, as suggested by the accelerator hypothesis.<sup>4</sup> In view of the current epidemic of obesity and the changing phenotype of T1DM in youths, distinguishing T1DM from T2DM based on phenotype and signs of insulin resistance has become a diagnostic challenge. Ketosis may be observed in such patients with double diabetes and thus it has been variably coined as type 1.5 diabetes or ketosis prone type 2 diabetes mellitus. It is important to note that patients with double diabetes may benefit from lifestyle modifications, including diet and exercise leading to weight loss which leads to improved insulin sensitivity. Management of T2DM in youths involve lifestyle modification and pharmacologic therapy. The ADA recommends 60 minutes of moderate to vigorous daily physical activity with strength training on at least 3 days per week.<sup>1</sup> Intake of nutrient rich, high quality foods and repudiation of sugar-sweetened beverages or fast foods is highly encouraged. However, adherence to a healthy lifestyle and nutritious diet remains troublesome to achieve among youths. Current pharmacologic therapy in young-onset T2DM is limited to the only FDA approved drugs, metformin and insulin.<sup>2</sup> In metabolically stable ( $A1C < 8.5\%$ ), asymptomatic patients without overt renal compromise ( $eGFR > 30 \text{ ml/min/1.73 m}^2$ ) or evidence of ketoacidosis at diagnosis, metformin is the initial drug of choice.<sup>1</sup> Insulin is indicated in youths with overt hyperglycemia (blood glucose  $\geq 250 \text{ mg/dL}$ ;  $A1C \geq 8.5\%$ ), osmotic symptoms, ketosis/ketoacidosis at presentation, or when a definite diagnosis of the type of diabetes is unclear.<sup>1</sup> While managing diabetes in adolescent females, it is important to consider polycystic ovarian syndromes and address comorbidities like sleep apnea and orthopedic complications associated with obesity. The Endocrine Society advocates several lifestyle changes involving physical activity and

nutritional modifications for treatment of young obese individuals. However, pharmacologic therapy in adolescents remains limited to Orlistat being the only FDA recommended drug between 12 and 16 years of age.<sup>5</sup> Although, Orlistat may cause reductions of BMI ( $0.7\text{--}1.7 \text{ kg/m}^2$ ), its success is limited by the increased number of dropouts among adolescents due to significant gastrointestinal side effects. In adolescent females, Metformin, though approved for treatment of T2DM patients  $\geq 10$  years of age, and those with PCOS, it is not yet approved for the treatment of obesity.<sup>5</sup>

## **OTHER FORMS OF DIABETES**

Several cases of monogenic diabetes may be encountered in adolescent clinical practice and needs special mention. Insulin secretion defects may be due to dominantly inherited mutations in the gene encoding glucose-sensing enzyme glucokinase or several transcription factors which affect beta-cell development and function, an entity known as maturity-onset diabetes of the young (MODY). It is noteworthy that despite a young age of onset, this form of diabetes is not insulin dependent. The major clinical categories of MODY are familial mild fasting hyperglycemia due to glucokinase gene mutations (GCK MODY), familial young onset progressive diabetes due to mutations of hepatocyte nuclear factor (HNF)  $4\alpha$  & HNF  $1\alpha$  (transcription factor MODY), and renal cysts and diabetes (RCAD) syndrome resulting from mutations in HNF  $1\beta$  gene. Diabetics younger than 25 years with strong family history of diabetes and phenotypes non-suggestive of T1DM or T2DM should be evaluated for MODY. Other disorders associated with insulin secretion defects include Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, deafness, neuropathic bladder, neurodegeneration, and ataxia), Wolcott-Rallison syndrome (early-onset diabetes, acute hepatic failure, spondyloepiphyseal dysplasia, developmental delay, and renal impairment), thiamine responsive megaloblastic anaemia (megaloblastic anaemia, non-autoimmune diabetes mellitus, sensorineural hearing loss), and mitochondrial

diabetes (diabetes, deafness, pigmentary retinopathy, cardiomyopathy, focal segmental glomerulosclerosis, myopathy, maternal inheritance). Presence of acanthosis nigricans in lean individuals with diabetes should raise suspicion of insulin resistance defects. Insulin resistance defects may be due to mutations affecting the insulin receptor (Type A insulin resistance syndrome, Rabson Mendenhall syndrome, Donohue syndrome); inherited lipodystrophies (Berardinelli Seip syndrome, Dunnigan variant, SHORT syndrome, mandibuloacral dysplasia, neonatal progeroid syndrome), or acquired forms of lipodystrophies. Childhood obesity syndromes like Alstrom syndrome (short stature, pigmentary retinal dystrophy, hypogonadism, sensorineural deafness, acute cardiomyopathy) and Bardet-Biedl syndrome (polydactyly, pigmentary retinal dystrophy, mental retardation, hypogonadism, renal impairment and short stature) may be encountered in adolescent females presenting with diabetes in clinical practice. Clinicians should be well-versed with these atypical forms of diabetes while treating adolescents, since management may vary widely depending on the underlying etiopathogenesis.

### **MENSTRUAL IRREGULARITIES, INFERTILITY, AND DIABETES**

T1DM is often associated with other autoimmune diseases like autoimmune thyroid disease, autoimmune adrenalitis (Addison's disease), and autoimmune hypophysitis which may adversely affect ovarian functions by speeding up oocyte loss resulting in primary or premature ovarian insufficiency. Anti-thyroid peroxidase (TPO) antibodies have been associated with unexplained infertility, implantation failure, early pregnancy loss, and an increased risk of preterm delivery.<sup>6-8</sup> With the concurrent evidences of anti-ovarian autoimmunity together with anti-thyroid and/or anti-adrenal autoimmunity, it is important to recognize these associations in patients of T1DM presenting with oligo-amenorrhoea and infertility in clinical practice. Thyroid hormones may also indirectly affect ovarian function via altered prolactin, GnRH,

and sex hormone binding globulins. Hypothyroidism may lead to hyperprolactinemia (enhanced TRH drive) which results in oligomenorrhoea, anovulation, and subsequent female infertility.<sup>9</sup> Autoimmune hypophysitis, again, almost always affects females of child-bearing age. It is most commonly diagnosed during pregnancy or during immediate postpartum period of autoimmune flare-up, often in association with patients of T1DM. Clinical manifestations may vary depending on the type of cell-line affected and may present with oligomenorrhoea/amenorrhoea and secondary infertility when gonadotroph function is impaired. Hyperprolactinemia-induced amenorrhoea/infertility may also occur in cases of isolated infundibulo-neurohypophysitis with impaired dopamine antagonism of prolactin. Elevated prolactin levels are also found in association with several autoimmune diseases like T1DM, autoimmune thyroid disorders, and Addison's disease.<sup>10,11</sup> PCOS (polycystic ovary syndrome), on the other hand, affects a large number of females of child-bearing age with consequent oligomenorrhoea, infertility, and insulin resistance. Chronic oligo-anovulation, biochemical or clinical hyperandrogenism, and polycystic ovaries on imaging characterize this disease. Peripheral insulin insensitivity and resultant hyperinsulinemia together with elevated luteinizing hormone (LH) levels lead to increased androgen production from ovarian theca cells. Elevated androgen hinders normal follicular maturation causing infertility. HAIR-AN (hyperandrogenism, insulin resistance, acanthosis nigricans) syndrome, a subset of type A insulin resistance may present with similar features and oligo-anovulation/infertility. With PCOS being the most common endocrine disorder in women of reproductive age, its co-occurrence with patients of T1DM changes the patient's phenotype, making it difficult to establish a definite diagnosis, and often mimicking "double diabetes." It is intriguing that autoimmune thyroid disorders are frequently associated with both PCOS and premature ovarian insufficiency (POI), which are functional opposites with respect to ovarian reserve and androgen levels. It is noteworthy

that T1DM may occur as a part of autoimmune polyendocrine syndromes (APSs), and AIRE gene mutation (APS-1) is known to be associated with autoimmune follicle depletion and premature ovarian senescence resulting in infertility.<sup>12</sup> Autoimmune adrenalitis (Addison's disease), a feature of APS (in association with T1DM) is most often associated with autoimmune oophoritis and subsequent ovarian failure.<sup>13</sup> Finally, uncontrolled hyperglycemia itself, may adversely affect female fertility as spontaneous ovulation is impaired. Although women with poor glycemic control often continue to ovulate, spontaneous ovulation improves with a better glycemic status.<sup>14</sup> Often, patients presenting with menstrual abnormalities and hyperglycemia may be secondary to other causes like acromegaly or Cushing's syndrome. While gonadotropin deficiency, hyperprolactinemia and/or low SHBG levels are implicated as causes of menstrual disturbances in acromegaly,<sup>15</sup> hypercortisolemic inhibition of gonadotropin release at hypothalamic level, rather than elevated circulating androgen levels is the probable cause of amenorrhoea in Cushing's syndrome.<sup>16</sup> In individuals with diabetes having a lean, non-obese phenotype, the possibilities of T1DM, MODY, LADA (latent autoimmune diabetes of adulthood), lipodystrophies, and insulin receptor resistance syndromes should be considered. In such patients, decreased serum leptin as a consequence to altered energy balance and/or body mass index may lead to functional hypothalamic amenorrhea (including anovulation, amenorrhoea, infertility) secondary to reduction of gonadotropin releasing hormone–luteinizing hormone (GnRH-LH) secretion.<sup>17</sup> Thus, in clinical practice, while evaluating diabetic females who present with menstrual disturbances and/or infertility, it is of utmost importance to ascertain the underlying cause and etiopathogenesis of such occurrence, lest important clinical associations be overlooked.

### **Contraception, Preconception, and Diabetes**

Contraceptive guidance as part of pre-pregnancy counselling is of utmost importance in women with diabetes, due to the heightened risk of congenital

malformations observed in unplanned pregnancies associated with poor glycemic control. Women with diabetes are usually well-motivated, and barrier contraception is considered both reliable and an acceptable form of contraception. In cases with high risk of user failure, hormonal contraception or intrauterine devices may be considered. Combined hormonal contraception (CHC) (oestrogen and progesterone) is considered safe in women with uncomplicated diabetes and has not been found to increase the incidence of diabetes in healthy, unaffected females.<sup>18–20</sup> CHC containing low doses of oestrogen (<35 µg of ethinyl estradiol) had negligible effects on blood glucose concentrations and insulin secretion. In diabetic females with evidence of micro/macro vascular complications, use of CHC was not associated with progression of disease or its complications.<sup>18,21</sup> However, CHC should preferably be avoided in diabetic women with evidence of microvascular complications (nephropathy with persistent proteinuria, severe retinopathy, active macular oedema) as risks outweigh benefits of its use [WHO medical eligibility criteria (MEC) 3/4].<sup>18,22–24</sup> On the other hand, progesterone-only pill (POP) is considered a safe option for diabetic women as benefits outweigh theoretical or proven risks with its use WHO MEC 2.<sup>22</sup> Long-acting reversible contraceptives (LARCs) include intrauterine device (IUD), intrauterine system (IUS), progestogen-only injectable contraceptives, progestogen-only subdermal implants, and combined vaginal ring. IUD and IUS were found suitable for use in women with diabetes.<sup>22,25</sup> Progestogen-only injectables (medroxyprogesterone acetate, norethindrone enanthate), however should be used with caution (WHO MEC 3/4) in diabetic females with microvascular complications, due to their adverse effects on lipid metabolism (reduced HDL levels).<sup>22,26</sup> Moreover, the use of emergency contraception, when necessary, is indicated as the benefits outweigh potential risks even in presence of severe vascular disease.<sup>22</sup> A Cochrane review analyzing randomized controlled trials regarding safety and efficacy of contraceptive use, observed

no significant differences between progesterone-only, combination hormonal, or non-hormonal contraceptives in diabetic women.<sup>20</sup> Combination hormonal contraceptives, in this review, were found to have negligible effects on glycemic stability.<sup>20</sup> Interestingly, the Missouri Pregnancy Risk Assessment Monitoring System (PRAMS) observed higher odds for gestational diabetes in women using hormonal contraceptive methods [adjusted odds ratio (AOR): 1.43; 95% CI, 1.32–1.55]. On the contrary, a protective effect was observed in women who had used barrier methods of contraception (AOR: 0.79; 95% CI, 0.72–0.86).<sup>27</sup> Women with T2DM who are planning pregnancy should be switched to insulin from oral drugs, which are known to cross placenta. In view of a mild increased risk of prematurity and lack of long-term safety studies, metformin should be stopped as soon as pregnancy is confirmed. In diabetic women with concurrent PCOS, the use of metformin have not demonstrated any benefit in preventing gestational diabetes or spontaneous abortion<sup>28</sup> and should be stopped when pregnancy is confirmed.<sup>29</sup> The importance of glycemic control should be emphasized with A1C levels <6.5% considered as optimal, as it is associated with lowest risk of congenital anomalies.<sup>30,31</sup> However, more often than normal, it is difficult to achieve optimum glycemic control while switching from oral drugs to insulin therapy. It is important to look out for concurrent use of glucocorticoids, often prescribed by gynecologists during preconceptional care, which may derail a successful attempt at achieving glycemic stability prior to conception. Preconceptional counselling visits should include standard tests for syphilis, rubella, HIV, hepatitis B virus, Pap smears, cervical cultures, and blood typing. Supplementation of prenatal vitamins (with at least 400 µg of folic acid) and cessation of smoking should be ensured.<sup>32</sup> It is important to review existing prescriptions for potential teratogenic drugs which need to be stopped. Biochemical evaluations for diabetes complications should be sought with specific testing for serum creatinine, urinary albumin-to-creatinine ratio, and A1C for ensuring optimum

glycemic control. A dilated eye examination with evaluation of retinopathy should be carried out prior to conception.<sup>32</sup>

## MENOPAUSE AND DIABETES

Post-menopausal and elderly women with diabetes are at increased risk of hypoglycemia, cognitive decline, functional disability, and usually have higher rates of comorbid illnesses such as hypertension and cardiovascular disease (CVD). A longer duration of diabetes with poor glycemic control is associated with worsening of cognitive abilities.<sup>33</sup> Thus, it is important to screen for cognitive impairment in females older than 65 years at initial contact and annually thereafter.<sup>34</sup> Hypoglycemia should be avoided in elderly females and glycemic targets should be individualized based on functional status, comorbid illnesses, and cognitive function. The Action to Control Cardiovascular Risk in Diabetes (ACCORD MIND) study did not reveal any significant benefits on cognitive abilities or brain structure following intensive glucose control.<sup>35</sup> Healthy individuals (with few coexisting chronic illnesses, intact cognition, and functional status) with longer life expectancy and without risk of recurrent hypoglycemia may benefit from a tighter glycemic control (A1C<7.5%). However, less stringent A1C goals (A1C <8.0–8.5%) should be exercised for individuals with multiple comorbid illnesses, functional dependence, impaired cognition, or limited remaining life-expectancy.<sup>34</sup> Metformin can be safely prescribed in patients with estimated glomerular filtration rate  $\geq 30$  ml/min/1.73m<sup>2</sup> and remains the first-line drug in elderly type 2 diabetic females.<sup>36</sup> Caution should, however, be exercised in patients with congestive heart failure or hepatic impairment due to enhanced risk of lactic acidosis. Sulfonylureas and insulin secretagogues, associated with high risk of hypoglycemia should at best be avoided. As elderly type 2 diabetics are at increased risk of CVD, thiazolidinediones (TZDs) may appear as an attractive agent either as monotherapy or in combination due to their beneficial role on serum lipids, hypertension, endothelial function, fibrinolytic

effects, and inflammatory biomarkers.<sup>37,38</sup> However, due to the property of fluid retention leading to dependent edema with the use of TZDs, it is contraindicated in those having established NYHA class III or IV heart failure and should be used with caution in elderly at risk of heart failure. There has been concerns regarding an increased rate of fractures with the use of TZDs. At a cellular level, a number of signalling pathways modulated by TZDs can adversely affect bone metabolism. With reduction of insulin resistance, circulating levels of insulin and amylin are lowered, both of which are anabolic to osteoblasts. Altered expression of adipocytokines, many of which have been suggested in regulation of bone metabolism may adversely affect bone health. A decrease in levels of circulating insulin-like growth factor 1 (IGF 1), which is crucial in osteoblast differentiation and proliferation might be detrimental to bone mass through inhibition of osteoblast formation. The various humoral factors associated with exposure to glucocorticoids, loop diuretics, or insulin and self-reported limited mobility increase the odds of fracture in T2DM patients treated with TZDs. Analysis of A Diabetes Outcome Progression Trial (ADOPT) observed an increase in fracture rates with use of rosiglitazone among pre- and post-menopausal women predominantly involving the lower and upper limbs. The cumulative incidence (95% CI) of fractures in women at 5 years was estimated to be 15.1% with rosiglitazone, 7.3% with metformin, and 7.7% with glyburide, reflecting hazard ratios (HRs) of 1.81 and 2.13 for rosiglitazone when compared with metformin and glyburide, respectively. In men, however, fracture rates were comparable between different treatment groups.<sup>39</sup> The Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) trial revealed significantly higher risk of fractures involving upper limbs and distal lower limbs especially, with use of rosiglitazone compared with active control in women (2.1 vs. 1.1 per 100 patient-years), but without any notable difference in men (1.0 vs. 0.8).<sup>40</sup> Post marketing safety analysis of pioglitazone by Takeda pharmaceuticals compared

patients treated with pioglitazone (n=8,100) versus non-TZD treated patients (n=7,400) from clinical trial database. It observed a significant increased risk of distal upper extremity (1.9/100 patient-years) and lower extremities fractures (1.1/100 patient-years) in women without any increased risk in men.<sup>41</sup> The PERISCOPE trial designed to compare effects of pioglitazone and glimepiride on progression of coronary atherosclerosis in patients with T2DM observed an increased risk of fracture rates in pioglitazone treated group (3.0%) compared to none in the glimepiride group (P=0.004).<sup>42</sup> A retrospective review of adverse events in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PRO active) trial found higher fracture rates in women treated with pioglitazone compared to placebo (1.0 vs. 0.5 per 100 patient-years) but not for men.<sup>43</sup> In patients of T2DM treated with TZD, increased risk of fractures was observed in women of all ages, but only in men older than 50 years of age.<sup>44</sup> Another study provided an additional insight into the association between TZD treatment and bone fractures in patients of T2DM, which observed postmenopausal women (>50 years) and a subset of men taking both loop diuretics and TZD were at increased risk for fractures.<sup>45</sup> Analysis of three healthcare registries, namely, the British General Practice Research Database (GPRD), the Dutch PHARMO Record Linkage System (RLS), and the Danish National Health Register revealed an increased risk of fracture for women exposed to TZDs: HR 1.48 (1.37–1.60) in GPRD, HR 1.35 (1.15–1.58) in PHARMO, and HR 1.22 (1.03–1.44) in Denmark. When combined, a 1.2- to 1.5-fold increased risk of fractures was observed for women using TZDs, but not for men, across the three databases.<sup>46</sup>

SGLT2 (sodium-glucose cotransporter 2) inhibitors may be convenient for elderly since they offer an oral route of therapy and are associated with significantly lower risk of death from cardiovascular causes, non-fatal myocardial infarction or stroke. However, their success is eclipsed by concerns of several adverse events associated with their use

in T2DM patients. Decreased proximal sodium reabsorption due to inhibition of SGLT2 receptors leads to an increased availability of sodium to be reabsorbed with phosphate via the  $\text{Na}^+ - 3 \text{PO}_4^{3-}$  co-transporter in the proximal tubules. The resultant mild increase in phosphate levels observed with SGLT2 inhibitor use is associated with increase in parathormone (PTH) and fibroblast growth factor 23 (FGF23) levels. Increased FGF 23 levels may decrease vitamin D concentration leading to diminished calcium absorption. The PTH-mediated increased bone resorption together with decreased vitamin D-mediated reduced calcium absorption may result in a diminished bone mineral density predisposing individuals to a higher risk of fractures. An increased risk of fractures have been observed in T2DM patients treated with canagliflozin after minor trauma and within first 12 weeks of therapy.<sup>47–49</sup> The canagliflozin and cardiovascular and renal events in type 2 diabetes (CANVAS) trial observed an enhanced rate of bone fracture among patients treated with canagliflozin when compared to placebo [15.4 vs. 11.9 event rate per 1000 patient-year,  $P=0.02$ ; HR 1.23 (0.99–1.52, 95% CI)], however this excess in bone fracture was not observed in CANVAS-R study (a study of the effects of canagliflozin on renal endpoints in adult participants with type 2 diabetes mellitus).<sup>50</sup> The increased fracture risk with canagliflozin may not be considered as a class-effect since the EMPA-REG (empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes)<sup>51</sup> trial and recent meta-analyses fail to confirm the adverse bone events with use of “gliflozins.”<sup>52,53</sup> On the other hand, the EMPA-REG trial observed an increased incidence of genital infections in patients treated with empagliflozin compared to placebo, but an overall predisposition for complicated urinary tract infections or pyelonephritis was not significantly different among treatment groups.<sup>51</sup> In the CANVAS study, an increased risk of genital infection (40 vs. 37 event rates per 1000 patient-years,  $P < 0.38$ ) and mycotic genital infection in women (68.8 vs. 17.5 event rates per 1000 patient-years;  $P < 0.001$ ) were observed in canagliflozin treated group compared to

placebo.<sup>50</sup> Thus, while prescribing SGLT2 inhibitors in postmenopausal women, it is important to counsel patients on proper genital hygiene.

### **HRT and Diabetes**

As many post-menopausal women undergo hormone replacement therapy to alleviate symptoms associated with menopause, the glycemic effects of combined oestrogen-progesterone therapy have long been debated. Several studies have evaluated the effects of postmenopausal hormone therapy on blood glucose levels and incident diabetes. Metabolic effects of oestrogen may be indirectly mediated through alterations of levels of insulin, catecholamines, or growth hormone.<sup>54–57</sup> While most clinical trials have failed to demonstrate any changes in fasting insulin levels with post-menopausal hormone therapy,<sup>58–62</sup> some reported reduced fasting or 3-hour postprandial insulin levels<sup>63–66</sup> or without significant excursions of insulin levels.<sup>67</sup> The heart and estrogen/progestin replacement study (HERS) observed lower fasting plasma glucose levels along with a 35% lower risk for incident diabetes in postmenopausal women on hormone therapy (incidence of diabetes 6.2% in hormone therapy group) when compared to placebo group [incidence of diabetes: 9.5% in placebo group;  $P=0.006$ , HR 0.65 (0.48–0.89; 95% CI)].<sup>68</sup> The postmenopausal estrogen/progestin interventions (PEPIs) study designed to evaluate effects of postmenopausal HRT on glucose metabolism, observed a significant decrease in fasting plasma glucose levels (2–3% decrease,  $P=0.03$ ) while an increase in 2 hour post-challenge glucose levels (2–7% increase,  $P=0.01$ ) was also recorded.<sup>69</sup> The woman’s health initiative (WHI) reported significantly lower rates of treated diabetes in women assigned hormone therapy than those in the placebo group (21% lower risk in the hormone therapy group at 1 year).<sup>70</sup> The NHANES III (Third National Health and Nutrition Examination) survey evaluating hormone replacement therapy and its relationship to glucose metabolism, observed lower levels of fasting glucose, fasting insulin, and glycated haemoglobin levels suggestive of a better glycemic control in diabetic women taking HRT.<sup>71</sup> The

evidence available on glycemic outcomes of HRT in post-menopausal women with T1DM is scarce. A study involving T1DM post-menopausal women on HRT observed no significant difference between hormone-treated group and placebo group.<sup>72</sup>

## Conclusion

The successful management of diabetes is a challenge to the treating physicians. Had it not been the case, the percentage of patients across the globe achieving the HbA1c target of less than 7% would have been much higher. The figure is even worse in India. Despite all the improvement in holistic diabetes care over the years, proportion of patients with satisfactory glycemic control has not changed from 2006 [37.8% in the Delhi Diabetes Community Survey (DEDICOM)] to 2014 (31% in the ICMR-INDIAB study). Managing diabetes in women in different stages of their lives pose further difficulties, both diagnostic and therapeutic.

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