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REVIEW ARTICLE

Laboratory diagnosis of pre and post-menopausal women with type 2 diabetes mellitus

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Abstract: Among the two types of DM, T2DM is prevalent among pre and post-menopausal women. Such women encounter many complications like MetS, IR, obesity, hypertension and atherogenic dyslipidemia. Although hormone replacement is the treatment to restore oestrogen, such treatment has its limitations. This review article brings out the recent research findings during the last 10 years on the prevalence, treatment options, usefulness of biochemical indices and improvement observed based on laboratory diagnosis. The contents of this review article will help future researches to undertake biochemistry analytes based diagnostic criteria to improve the T2DM status in such patients.

Key words: T2DM; DM; Menopausal; HRT; IR

Introduction

The number of people with Type 2 Diabetes Mellitus (T2DM) is on the increase and in India, approximately 35-40% are living with this disease. In uncontrolled T2DM, many complications such as Insulin Resistance (IR), metabolic syndrome (MetS) and oxidative Stress may follow. Of late, the prevalence of T2DM in women before and after menopausal are also on the increase. This review article highlights the recent findings in the clinical usefulness of biochemical indices in the above two type of patients.

With the growing incidence of both T1 and T2DM, the number of diabetic women of menopause age is on the rise in India. The risk of osteoporosis seems to be significant especially in T1DM patients, palliative treatment is the option for such menopausal symptoms. Transdermally administered estrogen is favorable in the therapy. The possible contraindications of hormone replacement therapy must, however, be accurately surveyed along with an assessment and treatment of risk factors for Cardio Vascular Diseases(CVD) prior to initiation of hormone therapy [1]. MetS is a complex disorder combining obesity, hypertension, atherogenic dyslipidaemia and IR, a clustering of factors which markedly enhance the risk of developing CVD and T2DM. Main features of the MetS, which are found in many postmenopausal women, are increasing prevalence of IR and obesity (particularly visceral adiposity). Accordingly, a majority of postmenopausal women comply with criteria defining the MetS and CVD is the first cause of morbidity/mortality in women, occurring even more frequently than in men. Moreover, obesity-related T2DM approaches pandemic proportions. Simultaneous occurrence of IR and obesity are most detrimental for metabolic health, and are also associated with increased oxidative stress, inflammatory and prothrombotic processes as well as with postmenopausal alterations in adipocytokine production. Hormone replacement therapy (HRT) is a better option and provides the selected progestin does not antagonize estrogen action, may improve fat mass and distribution, dyslipidaemia and insulin sensitivity in postmenopausal women [2].

During menopause, women's body composition, sex hormone profile, and metabolic profile may change dramatically. The evidence linking menopausal and sex hormone changes with increased diabetes risk is weak, although rapid changes as observed with oophorectomy may increase risk. Further studies should investigate the contradictory effects of HRT upon hepatic and glucose metabolism in mid-life women [3]. Many post-menopausal women live with DM; however, little information is available about how the changes that occur around the time of menopause might uniquely affect management of DM in this population. Although weight gain that commonly occurs during the menopausal transition is largely attributable to aging rather than the transition itself, changes in body composition have been independently associated with menopausal status. These changes in body composition have, in turn, been associated with alterations in insulin sensitivity and glucose metabolism in postmenopausal women. HRT seems to have neutral or beneficial effects on the adverse changes in body composition associated with menopause. Whether menopausal status independently influences diabetes risk remains controversial. Nevertheless, consistent findings from large clinical trials suggest that HRT in postmenopausal women decreases the risk of developing DM. Similarly, many studies suggest that HRT in post-menopausal women has neutral or beneficial effects on glycemic control among

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women already diagnosed as having DM. Hence studies are needed to elucidate the mechanisms that underlie these relationships and to determine how these observations should influence recommendations for the care of post-menopausal women with DM [4].

Serum adiponectin levels have been suggested to be the predictor of T2DM in diverse populations. However, the relationship between circulating adiponectin levels and the risk of development of T2DM in post-menopausal women has not yet been investigated. Women with T2DM had lower adiponectin levels than the healthy post-menopausal women. Multiple regression analysis showed that, after adjustments were made for age, cardiovascular risk factors, osteoprotegerin (OPG), and high-sensitivity C-reactive protein (hs-CRP) levels, higher baseline adiponectin levels were associated with a lower relative risk (RR) of having T2DM confidence interval. Higher baseline adiponectin levels functioned as a predictor of a lower risk of developing T2DM among post-menopausal women during a 5.8 years follow-up study. Therefore, it is suggested that elevated adiponectin levels may offer protection against the development of T2DM after the menopause [5]. Plasma total homocysteine (tHcy) concentration is independently associated with the occurrence of osteoporosis in postmenopausal patients with T2DM and future prospective studies are warranted to clarify the relationship [6].

LRP5 gene is an impressionable gene in postmenopausal women with osteoporosis (OP) in Shanghai. T2DM patients have a high Bone Mineral Density (BMD) when compared with controls, which may be related to Body Mass Index (BMI). LRP5 genotype is not an impressionable gene in postmenopausal women with T2DM in Shanghai [7]. Low bone turnover in patients with T2D and highlight the potential detrimental effects of prolonged hyperglycemia on bone quality. Thus, the skeleton needs to be recognized as another important target tissue subject to diabetic complications [8]. Increased serum sclerostin and decreased serum Insulin-like growth factor 1 (s-IGF-1) were associated with vertebral fractures (VFs) among post-menopausal women with T2DM, suggesting that sclerostin and/or IGF-1 may be involved in increased bone fragility in T2DM and could be potential markers of VF severity [9]. The presence of Hypertension (HT) increases VF risk independent of blood pressure levels, anti-hypertensive medications, or falls, and that calcium channel blocker (CCB) treatment increases both VF and non-VF risks possibly via falls in T2DM post-menopausal women [10].

Improvement in LDL-C did not correlate with percent improvement in bone metabolism or bone quality markers. Raloxifene, unlike estrogen, improved LDL-C and decreased homocysteine, indicating that raloxifene can potentially improve LDL-C as well as bone quality in post-menopausal women with T2DM [11]. Using ethnicity-specific single nucleotide polymorphisms (SNPs) as randomization instruments, no statistically significant association between Telomere Length (TL) and diabetes risk were observed. Although leukocyte TL was weakly associated with diabetes risk, but the association was not independent of known risk factors. These prospective findings indicate limited clinical utility of TL in diabetes risk stratification among post-menopausal women [12]. Among the metabolic syndrome components, low osteocalcin levels had significant associations with elevated blood glucose and elevated waist circumference in multivariate analyses. Serum osteocalcin was independently associated with glucose intolerance and abdominal obesity as the components of MetS and T2DM in post-menopausal women. Since CrossLaps and alkaline phosphatase levels were independently associated with the presence of T2DM, the unique contribution of osteocalcin in glucose metabolism could not be concluded [13].

Circulating Osteoprotegerin (OPG) levels are significantly associated with diabetes, independent of cardiovascular risk factors in postmenopausal women. However, OPG levels have no correlation with the MetS or its components. Further studies are warranted to determine the pathophysiologic origin of elevated OPG in T2DM [14]. Estriol treatment resulted in a rise of vaginal health index (VHI), appearance of lactobacteria in the vaginal smear, lowering of atrophic vaginitis detection rate. No significant changes were registered in the controls. Thus, local estriol administration effectively prevents and treats VHI in post-menopausal females [15]. After multivariable adjustment, low-fat dairy product consumption was inversely associated with the risk of T2DM. RR was roughly 0.5-0.6 in the upper quintiles compared with the lowest quintile (median servings/d, 2.8 in the 5th quintile and 1.5 in the 4th quintile vs. 0.05 in the first quintile; P-trend. The inverse relationship was more pronounced in women with a higher BMI. High yogurt consumption was associated with a significant decrease in diabetes risk, whereas there was no relationship between high-fat dairy product consumption and diabetes risk. A diet high in low-fat dairy products is associated with lower diabetes risk in post-menopausal women, particularly those who are obese [16].

Diabetes attenuates the HRT-related increase in atheroprotective HDL α1 particles. Faster progression of coronary atherosclerosis in women with diabetes could be mediated in part by a worse lipoprotein profile in these women than in women

without diabetes, both before and during HRT [17]. Women with diabetes who received oral HRT and women who received HRT plus Vitamin C and E (VCE), there was a significant fall in urea, uric acid, creatinine, total bilirubin, conjugated bilirubin, AST, ALT, LDH values. There was no significant change in red blood cell counts, total protein, albumin, sodium, potassium, hematocrit, hemoglobin and free thyrotoxine and triiodothyronine values in post-menopausal women with diabetes or treated with oral HRT and VCE. Hence, daily VCE and HRT administrations seem to produce significant improvement on biochemical parameters in the blood of post-menopausal women with T2DM. The HRT and VCE supplementations may strengthen the antioxidant defense system and they may play a role in preventing kidney and liver diseases of post-menopausal women with T2DM [18].

Diabetes and the menopause are two independent risk factors for development of CVD. Risk factor modification in terms of diabetes appears straightforward; however, correction for oestrogen deficiency which hallmarks the menopause appears complex. The low-risk diabetic post-menopausal women should be offered appropriate HRT, whereas non-oestrogen-based treatments should be the treatment of choice for high-risk women [19]. It seems reasonable to argue that while dealing with post-menopausal diabetic women, clinicians should consider obesity measures, lipids and dietary fatty acids simultaneously to better comprehend clinical assessments and risk stratification [20]. A combined strength and aerobic training program could induce positive adaptations on lipid profile, glycemic control, IR, cardiovascular function, and physical fitness in post-menopausal women with T2DM [21].

BMD and its association with BMI are uncertain in post-menopausal women with T2DM in mainland China. The osteoporosis risk was higher for the hip than for the lumbar spine, especially in DML, indicating that post-menopausal women with T2DM had higher BMD and lower osteoporosis risk in the lumbar spine, and that lower BMI was an indicator of osteoporosis in mainland China [22]. At multivariate analysis, menopause was an independent correlate of tHcy concentration, together with creatinine, folate and MTHFR genotype. Menopause has a strong influence on tHcy concentration even in T2DM women and demonstrate, for the first time, that it may modulate the association between tHcy and the common MTHFR polymorphism both in diabetic and non-diabetic women [23]. Serum DHEA-S concentration correlated positively with bone mass, whereas glycemic control, BMI, or duration of diabetes did not correlate with bone mass or urinary N-Telopeptide Crosslinks (NTx) concentration in postmenopausal women with T2DM [24].

Serum DHEA-S level seemed to be associated with atherosclerosis in diabetic post-menopausal women independent of age, body stature, diabetic status and other atherosclerotic risk factors, and might be a useful addition to other parameters for assessing the risk of atherosclerosis in this population [25]. The interactions among estrogen, menopause and cardiovascular risk bring forth the question of whether the HRT affects IR or not. Studies so far have yielded controversial results. The overall results of recent reports indicate that post-menopausal HRT improves IR. However, the available evidence is not strong enough to suggest the use of post-menopausal HRT as a first-line therapeutic measure in the management of IR [26]. Elderly, post-menopausal, osteoporotic obese women with T2DM are resistant to long-term bisphosphonates, especially in regions of the hip, femoral neck and forearm compared with the spine. The efficacy of bone resorption inhibitors in patients with T2DM, especially in comparison with anabolic agents, should be considered in future studies [27].

Hypoadiponectinemia in post-menopausal women may be explained by only IR because the amelioration of whole-body insulin action by 6-month Metformin therapy leads to increase plasma adiponectin levels; leptin levels did not significantly change after 6-month Metformin therapy [28]. Diabetic women have lower adiponectin levels compared to healthy women. HbA1c as an indicator of glycemic control has a negative correlation with serum adiponectin. Adiponectin may play an important role in the pathogenesis of diabetes, and may be an independent predictor of the development of diabetes in women [29]. IR, believed to be a key pathogenic factor in both Poly Cystic Ovarian Syndrome (PCOS) and the MetS, may be the thread that links the two conditions. Menstrual health in adolescents could be viewed as yet another component in the evaluation of the MetS. Careful assessment of menstrual history and appropriate laboratory work-up could reveal the presence of PCOS in obese at-risk adolescent girls with a family history of the MetS [30].

An increased prevalence of female sexual dysfunction (FSD) has been reported in women with DM. Cardiovascular and neurological impairments are associated with FSD in diabetic women. Follow-up studies are required to evaluate sexual dysfunction as a risk factor for future cardiovascular or neurological events [31]. Urinary albumin excretion is independently associated with current smoking in Japanese premenopausal with T2DM, confirming that current smoking is

associated with an increased level of urinary albumin excretion and smoking as a risk factor in the development of increased urinary albumin excretion in these patients [32].

The reduction in carotid intima medial thickness progression developed gradually occurred only in women who had an increase in insulin sensitivity, and was unrelated to the presence of the MetS at baseline. Troglitazone reduced the progression of subclinical atherosclerosis via a mechanism that involved unmeasured mediators of atherosclerosis, either in the circulation or directly in the arterial wall [33]. In subjects who have not undergone hormone replacement therapy and whose age at menopause is greater than 49 years, an increase in years since menopause confers a negative influence on glucose tolerance and increases the risk of IGT by 6% for each year after menopause [34].

Conclusions

This review article highlights the clinical usefulness observed in changes of some special biochemical markers such as adiponectin, tHcy, IGF-1, osteocalcin and VCE in order to differentiate women with pre and post-menopausal suffering from T2DM. Although HRT is said to restore some of the above markers to normal, it does not help to differentiate DM status in post-menopausal women. The content of this review article will help future researchers to design a list of laboratory tests for the diagnosis of pre and post-menopausal women with DM.

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