Incidence of diabetes in Asian population and diabetic bone quality

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Abstract

Diabetes mellitus (DM) is characterized by high blood glucose levels and divided into two types, type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T2DM known as non-insulin dependent diabetes, which is due to insulin resistance and relative deficiency. World Health Organization (WHO) estimated the prevalence of diabetes for all age groups worldwide will be doubled in in 2030. Shockingly, the Bureau of Non Communicable Disease of Thailand found similar trend for Thai population. They claimed that it could be caused by changes of the style of food consumption specially popularity of the western like diets that contain high fat and sugar. Apart from the classical complication of diabetes such as cardiac failure, diabetic nephropathy, peripheral neuropathy, adverse effects associated with bone health become increasing apparently. Despite a number of studies in biological alteration of skeleton affected by chronic hyperglycemic diabetes, the association between DM and osteoporosis remained controversial. This review focused on the incidence of diabetes mellitus in Asian population as well as the metabolic abnormalities of DM potentially affecting bone metabolism, structures and mineral density.

Key words: asian population, bone mass, bone mineral density (BMD), the diabetes prevention program (DPP), non communicable disease, metabolic abnormalities

Introduction

Diabetes mellitus (DM) is characterized by high blood glucose levels and divided into two types, type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM commonly found in juveniles and young adults can be called juvenile diabetes. T1DM is insulin dependent diabetes. T2DM is normally found in adults or older people, it is also known as non-insulin dependent diabetes which is due to insulin resistance and relative deficiency. Both type of DM with chronic hyperglycemia usually review sign and symptoms of neuropathy, retinopathy and nephropathy.

DM is a critical and chronic metabolic disease with high incidence all around the world. World Health Organization (WHO) estimated the prevalence of diabetes for all age groups worldwide will be increased from 171 million in 2000 to 366 million in 2030. The National Institute of Health (NIH) had reported the percentage of people with diabetes in United States become double in April 2014. Moreover, DM is referred the seventh leading cause of death in USA. About 13 million or 11.8% of all men aged over 20 years or older and 12.6 million or 10.8% of all women aged 20 years or older are diabetic. In addition, the Bureau of Non Communicable Disease of Thailand found the increased rate of Thai prevalence of diabetes from 2008 to 2010 is similar to that of United States. This problem could be caused by changes of the style of food consumption, especially a popularity of the western like diets that contain high fat and sugar content.

The Center for Disease Control and Prevention (CDC) reported that obesity and lack of physical activity causes approximately 33% increased diabetes risk in the southeast region in US. The pathogenesis of T2DM was believed to be dependent on being overweight and the lack of physical activity. In 2011, Admiraal and his co-workers found significant association between physical inactivity and T2DM in Caucasians. They reported a prevalence of T2DM varies among ethnic groups is secondary to their levels of physical activity. Another study in Atlanta found a contribution of obesity to an increased incidence of diabetes in United States from 1976 to 2004. The number of obese persons had been represented the increase in national diabetes prevalence in United States over the past 25 years. It might be a reflection of the rapid population increases in prevalence at the high end of the Body Mass Index (BMI) distribution, integrated with the strong causal link between diabetes and obesity.

Treatment of T2DM is varied because of the side effects of the anti-diabetic drugs and multifactorial causes in DM. Anti-diabetic drugs such as sulfonylureas, meglitinide mainly causes hypoglycemia as a serious side effect. Thiazolidindiones, pioglitazone or rosiglitazone act as agonists of the peroxisome proliferator activated receptors (PPAR-γ) which are effective anti-diabetic drugs, however their side effects such as fluid retention, increased cardiac failure and osteoporosis are cautious. Biguanides is another choice of anti-diabetic drug but it has side effect such as lactic acidosis in DM patients who has increase risk of liver or renal function impairment. Alpha-glucosidase inhibitors also affect the liver function and cause flatulence and diarrhoea which may lead to hypoglycemia.

Some evidence suggested that there are deteriorating effects of DM on bone that may increase fracture risk of DM patients. Decreased bones mass in diabetic patient usually causes greater risk of fracture. So the fracture healing delayed in DM due to the fusion of increasing cartilage resorption and decreasing bone formation. The cellular and
molecular levels responses in T1DM and T2DM are different according to level of Insulin Growth Factor 1 (IGF1) which is dominant inducers of cell growth and development\textsuperscript{10-12}. Alternatively, different time course of type 1 and 2 DM might contribute to their different outcomes and prognosis\textsuperscript{13}. The diagnostic criteria for DM can be performed by at least 3 methods based on plasma glucose level shown in Table 1.

Type 1 Diabetes Mellitus (T1DM)
This is also known as juvenile onset diabetes because the disease has normally developed in adolescence or childhood. T1DM is caused by autoimmune reaction where the host immunity attacks its own pancreas resulting in defect of insulin production from β-cell which leads to β-cell dysfunction and hypoinsulinemia. The T1DM patient is successfully treated by exogenous insulin as it can sufficiently rescue the hyperglycemia to the normal level. T1DM sometimes demonstrates adverse effects on the bone and skeletal development. For instance, the articular cartilage area at knee joint was found to be reduced, due to loss of the cartilage surface\textsuperscript{9}.

Type 2 Diabetes Mellitus (T2DM)
T2DM is known as non-insulin dependent diabetes, currently affect more than 10 million U.S. citizens aged 65 years or above\textsuperscript{1}. The Asia pacific region had been considered to be the major area of the rapidly emerging epidemic of T2DM because of the greater population of this region\textsuperscript{14,15}. Among the 10 leading countries like USA, India, China were reported to have a prevalence of diabetes, they estimated that 5 of them will be in Asia by year 2025. T2DM is a common type of diabetes and increasingly prevalent illness that can be largely preventable. According to WHO, T2DM comprises 90% of people with diabetes around the world\textsuperscript{16,17}. Nowadays, the evidence suggested that there is an increased incidence of T2DM in children and adolescent as well\textsuperscript{17-19}.

In Australia, among the young age, the risk of T2DM rose with increasing age from an average annual rate of new cases of 3/100,000 population in 10–14 year olds, to 8/100,000 for those aged 15–19 and 16/100,000 for those aged 20–24\textsuperscript{20}. Primary prevention measures can be directed to the high-risk individual or the overall population of children. Prevention of T2DM in the high risk adolescent and children is required proper identification of them and provide the accurate service they need. This wide spread of T2DM occurred may due to the western style of food consumption that contain a lot of sugar and fat\textsuperscript{21,22}, obesity or overweight\textsuperscript{23,24} and lack of physical activity\textsuperscript{25,26}. T2DM is insulin resistance, which means the body can make

<table>
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<th>Table 1</th>
<th>Criteria for diagnosis of DM according to American Diabetes Association, 2013.</th>
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<tr>
<td><strong>Diagnostic Methods</strong></td>
<td><strong>DM Criteria</strong></td>
</tr>
<tr>
<td>Fasting plasma glucose (FPG)</td>
<td>- Normal fasting glucose</td>
</tr>
<tr>
<td></td>
<td>- Impaired fasting glucose (IFG)</td>
</tr>
<tr>
<td></td>
<td>- Provisional DM</td>
</tr>
<tr>
<td>Oral glucose tolerance test (OGTT)</td>
<td>- Normal glucose tolerance</td>
</tr>
<tr>
<td></td>
<td>- Impaired glucose tolerance (IGT)</td>
</tr>
<tr>
<td></td>
<td>- Provisional DM</td>
</tr>
<tr>
<td>Glycosylated hemoglobin (HbA1C)</td>
<td>- Normal glucose</td>
</tr>
<tr>
<td></td>
<td>- Provisional DM</td>
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insulin but body cannot respond to insulin. Thus, glucose from the food intake cannot be utilized in the cells leading to insulin resistance of the peripheral tissue. The body would adaptively produce more insulin to amend for this effect, which therefore results to hyperinsulinemia. Patients can be found preserved normal glucose tolerance (NGT), normal plasma glucose or lower level than 100 mg/dl at this stage. However, if the raised plasma glucose still goes on, β-cells of the pancreas would not be able to continue producing excessive level of insulin. Afterward, dysfunction of β-cell and deficiency of insulin will be emerged in this type of DM. All of above, these characteristics would develops the T2DM patient with chronic hyperglycemia. The etiology of T2DM is associated with obesity, aging and genetics. Recently, western-foods consumption and sedentary lifestyle are also contributing factors of T2DM. The ethology of T2DM development is shown in Figure 1.

It is proved that obesity substantially increased risk of diabetes in one lifespan. The division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion did a survey among 37,606 adults aged 20 to 74 years between 1976-1980 and 1999-2004 in US. They reported increased of DM preference from 5.08 % in 1976-1980 to 8.83 % in 1999-2004. This study revealed that 3.7 % of total cases additionally existed in 1999-2004 compared to 1976-1980. The result is shown in Table 2. This survey implied that the increased prevalence of Diabetes in United States over recent decades is due to the high level of obesity.

**Figure 1** The natural ethology of T2DM. The right panel demonstrates the pathological condition of each stage.
The WHO expert consultation reviewed scientific evidence that Asian populations have different associations between BMI, percentage of body fat, and health risks than those of European populations. The proportion of Asian with a high-risk of T2DM and cardiovascular disease is substantial at lower BMIs of WHO cut-off point for overweight (25 kg/m²)²⁷. Some studies survey a body composition in various Asian populations such as Hong Kong Chinese²⁸,²⁹, Singaporean Chinese, Malaysian and Indians³⁰, Indonesians³¹ and Japanese³² they demonstrated that Asian have a high percentage of body fat with a low BMI. It has been shown that the relative percentage of body fat is varied in all population of different of BMI. These factors include environmental factors, such as the amount of physical activity, as observed in the differences between rural and urban populations such as in India and Thailand. Evidences also suggested that a combination of low BMI and high percentage of body fat, is associated with increased risk of diabetes and heart disease in Asian populations²⁷. It was reported in Hong Kong and Singapore²⁹,³³ population that the risk of cardiovascular disease or T2DM is high in their populations with low BMI. Moreover, data from Chinese population showed that the prevalence of hypertension, diabetes, dyslipidemia, and clustering of risk factors are all increased with decreasing of their BMI; below the cut-off point for overweight (ie, 25 kg/m²)³⁴. The WHO consultation also acknowledged that, Asians have a low proportion of fat mass to lean mass compared with Europeans, while they have a higher prevalence of diabetes²⁷.

### Diabetes Mellitus prospects in Asian population

Diabetes Mellitus is now a global public health threat and a major lifestyle disorder, the prevalence of which is increasing globally. More than 60% of the world’s diabetic population is contributed by the Asian population as well as the prevalence of diabetes is increasing in Asian countries at the moment. In Europe, Admiraal and coworkers performed a cross-sectional study under the supervision of Netherlands Study on Health and Ethnicity in 35-60 years old people among them 508 were Caucasian, 596 African and 339 Hindustani participants. They found a significant association of physical inactivity with T2DM in Caucasians after adjustment of multiple risk factors such as sex, age, BMI, ethnicity, hypertension and smoking, history of cardiovascular disease, educational level and having first-degree relative with DM⁴. This study therefore suggested that physical inactivity can majorly contribute to the development of T2DM. However, a number of evidences reported that 80% of the T2DM patients in India, China and Japan did not

### Table 2 Percentage of population in US categorized obesity by their body mass index according to US National Center for Chronic Disease Prevention and Health Promotion

<table>
<thead>
<tr>
<th>Percentage (%)</th>
<th>Normal or Obese</th>
<th>Body Mass Index (BMI)</th>
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<tbody>
<tr>
<td>8%</td>
<td>Normal or below normal</td>
<td>BMI &lt;25</td>
</tr>
<tr>
<td>27%</td>
<td>Over weight</td>
<td>BMI-25 to 30</td>
</tr>
<tr>
<td>32%</td>
<td>Class I Obesity</td>
<td>BMI-30 to 35</td>
</tr>
<tr>
<td>23%</td>
<td>Class II Obesity</td>
<td>BMI-35 to 40</td>
</tr>
<tr>
<td>26%</td>
<td>Class III Obesity</td>
<td>BMI &gt;40</td>
</tr>
</tbody>
</table>
show high BMI or characterized obesity. Evidence suggested that socio-economic growth and industrialization are rapidly occurring in many of Asian countries which spreading urbanization widely, adversely affecting the lifestyle of populations. Asians have reported to have a lower thresholds for the environmental risk factors and strong ethnic and genetic predisposition for DM which means that they could develop diabetes sooner at a younger age with lower BMI and lesser waist circumference when compared with those in Western population. The superlative rates of urbanization (50%) have been found in Singapore, Korea, Malaysia, Philippines and Indonesia. China, Pakistan and India. Thailand, however, was shown in intermediate rates (30%) while Bangladesh and Sri Lanka have low rates of urbanization, respectively. They reported the adverse effects of urbanization such as decreasing physical activity, shifting diet habits towards high-energy foods and accumulation of upper body adiposity aggravates the developing of DM. The recent studies demonstrated that a living pattern of the rural population in India and China have altered which causes an increase of total prevalence of overweightness and diabetes in these countries. Furthermore, the prevalence of diabetes was recently reported 10 times-increased among Chinese adults, as from lesser than 1 % in 1980 to almost 10 % in 2008.

Another cohort study had done in four Asian countries i.e., India, China, Japan and Singapore to revise WHO’s criteria for diabetes in Asian people, which included 10,851 men and 13,844 women age ranged between 30-89 years old. They challenged the plasma glucose by oral glucose tolerance test (OGT). The results demonstrated among these countries, India showed the highest prevalence of T2DM and the age peak prevalence for DM for Indian subjects were 60-69 years whereas Chinese and Japanese were 70-89 years. This study suggested that aging in any population or races could also contribute to T2DM. In spite of well distinguished pathophysiological changes such as hyperglycemia and other correlated complications, some studies had reported damaged bone metabolism in DM, like a reduced BMD of femoral neck and elevated risk of fracture of femoral neck and lumbar. Conversely, some other studies suggested an increased BMD as well as increased the risk of fracture in T2DM patients. Hence, how the bone structure is affected in T2DM and what the pathogenesis could be, these are still under discussion.

Changes in bone and cartilage development in T2DM

Apart from the classical complication of diabetes such as ischemic cardiac failure, diabetic nephropathy, peripheral neuropathy, adverse effects associated with bone health become increasing apparently. The healing process of hard tissue among DM patients is delayed. Impairment in bone formation/turnover is associated with the metabolic abnormalities in T1DM and T2DM, of which increases the risk of osteoporosis. One of the major complications of diabetes is diabetic osteopathy, decrease in bone quality or low stress fracture. Some of the evidence strongly revealed that the main pathological mechanism of diabetic osteopathy is an excess accumulation of advanced glycation end products (AGEs) on collagen of bone extra cellular matrix (ECM). Chronically uncompensated T2DM and aging elevate circulating reactive oxygen species, glucose or carbonyl stress which can influenced excess formation of AGEs on bone ECM. Aggregation of this collagen-AGEs decrease bone quality, strength, post-yield strain and energy, fracture resistance and toughness. Also bone marrow
mesenchymal cells, osteoblasts and osteoclasts express receptor like RAGE that can bind AGEs with high affection, altering natural cellular homoestasis. This collagen-AGEs interact with RAGE diminishes the osteogenic potential of mesenchymal cells, reduces the osteoblastic bone forming capacity and develops a long term reduction in osteoclastic recruitment and bone-resorbing activity. These cause decrease bone turnover with greater accumulation of AGEs thus increasing fracture risk\(^4\). In 2008 Kayal and his team had worked on diabetic CD-1 mice to investigate the mechanism by which DM may affect fracture healing and they focused on the transition from cartilage to bone a middle point of fracture healing process. Femoral fracture was induced in all mice, one group of diabetic mice had received insulin treatment through slow released insulin implants. They noticed that on day 16, the chondrocyte apoptosis was significantly increased in experimental mice and this effect was blocked by insulin. The amount of bone formation within the callus of diabetic mice was significantly less than the normal mice on day 16 and 22 but could be brought to normal level by insulin treatment. This study indicated that a significant effect of DM on fracture healing is increased chondrocyte apoptosis and osteoclastogenesis which stimulate the loss of cartilage and decrease the anlage for endochondral bone formation during fracture repair. Results from this study also suggested that insulin effects directly to inverse the adverse effects of DM during fracture healing\(^9\). Although the metabolic abnormalities of DM potentially affect bone metabolism, structures and mineral density, the extent of their contribution to osteoarthritis with T2DM is still under debated\(^41,45,46\).

The vitro studies of insulin effects on chondrocytes found that insulin effects are varied in different organs, type of cells and dose of insulin treatment. In 2003, Torres and co-workers used three dimensional mesenchymal cells of chicken embryonic culture to prove that insulin with the concentration of 60 mg/mL (10 nM) induced cartilage formation by promoting cell proliferation and also caused impaired chondrocyte maturation, chondrocyte apoptosis and decreased the activity of alkaline phosphatase, which plays the main role in mineral deposition. So they suggested that this dose of insulin might enhance cartilage formation but delay the longitudinal bone formation\(^47\).

In 2011, Wu and his group demonstrated that insulin affects to the development of chondrocytes in a dose-relevant manner, the proliferation and differentiation of chondrocytes were enhanced by the insulin receptor in the presence of recombinant human insulin (100-100 nM). Furthermore, they found similar results in the organ culture of fetal mouse metatarsal bones. These studies concluded that the action of insulin partly promotes bone and cartilagenous growths\(^48\).

In T2DM patient, Liefde and coworker suggested that DM exhibits osteopenia that contributes an increase of fracture risk. They had measured the BMD of femoral neck and lumbar spine of 6,655 men and women aged 55 years old. Surprisingly, subjects with DM had higher BMD when compared to non-DM subjects. However, the two DM groups (treated DM or IGT) showed a persistently increased fracture risk despite their higher BMD. The authors suggested the fracture risk might be due to long-term complications associated with DM\(^43\). The higher baseline BMD diabetic white women, but not men or black women, had more rapid bone loss at the femoral neck than those with normal plasma glucose level has been reported in cohort study. This increased bone loss may
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contribute to the higher fracture risk observed in older diabetic women49. Moreover, a review study on bone metabolism and fracture risk in T2DM reported that the prevalence of osteoporosis in T2DM is high in western countries. Meta-analysis of multiple studies showed the hip fracture risk in T2DM patients were increased from 1.4 to 1.7 folds, though the BMD of these patient did not decreased. Moreover the vertebral fracture risk was shown increased while BMD was unchanged. As mentioned above, these studies indicated that BMD is not the only mutual indicator for assessing the risk of fracture in DM patients. They suggested that bone fracture risk of T2DM depended on bone quality deterioration more than bone mass reduction, therefore, the etiology of DM-related bone fragility and diagnostic markers other than BMD need to be explored42,49.

During T2DM progression, the delayed fracture healing occurs due to combined cartilage resorption and decrease bone formation. Insulin treatment was reported for rescued effects on the osteoblast proliferation, chondrogenesis, mineralization and mechanical strength of T2DM fracture healing in animal model. Therefore, the defect of the fracture healing in T2DM was suggested to be mediated by hyperglycemia. This study confirmed that there were catabolic events that normally occurred in fracture healing and they were significantly aggravated by T2DM, however, they could be partially reversed by reducing blood glucose under the insulin treatment9.

Discussion

The information presented in this study provides an understanding of diabetic bone pathology as well as its cartilaginous changes in T2DM. In T2DM patients, the relationship between serum markers and bone metabolism has been documented only a few studies. By BMD itself, it shows a low sensitivity and poor prediction of fracture in osteopenic range (people who have BMD value between -1 to -2.5). We need additional markers of which are potential candidates for such purposes, it is unclear if they could predict the occurrence of new fractures in T2DM patients in a prospective fashion. WHO has developed a recent fracture risk assessment called “FRAX” algorithm. This is a computer-based algorithm that implements models for the determination of fracture probability in all gender and various fracture risk. These factors are involved age, sex, a prior fracture, a family history of fracture, smoking and lifestyle risk etc. The programme also designated for using in different models and countries. More importantly, it is available online and easily accessible (www.shef.ac.uk/FRAX).

Nevertheless, the “FRAX” only should not be used solely to consider as a gold standard but it clearly is a new platform technology to detect the feasibility of fracture50. By integrating the influence of several well-validated risk factors for fractures together with BMD measurement, this algorithm will be useful for the case-finding strategy that identifies diabetic patients at high risk for fracture.

Funding: This study was supported by Mahidol University, Master degree program of Oral Biology, Faculty of Dentistry, Mahidol University and Thailand Research Fund (TRF) to D. Seriwatanachai

Conflict of interest: The authors claim no conflict of interest.

Ethical Approval: None

References

1. National diabetes fact sheet: national estimates and general information on diabetes and
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25. Nesmith J. Type 2 diabetes mellitus in children


International Abstract

2-Dimensional changes of the soft tissue profile of augmented and non-augmented human extraction sockets: a randomized pilot study
Filüge T, Nelson K, Nack C, Stricker A, Nahles S.
2-Dimensional changes of the soft tissue profile of augmented and non-augmented human extraction sockets: a randomized pilot study.

Aim: This study identified the soft tissue changes of the alveolar ridge at different time points within 12 weeks after tooth extraction with and without socket augmentation. Materials and Methods: In 38 patients with single tooth extractions, 40 sockets were augmented and 39 extraction sockets were not augmented. At 2, 4, 6, 8 and 12 weeks impressions were taken and casts digitized with a laser scanner. The horizontal and vertical changes were compared between augmented and non-augmented sites. A p-value <0.05 was considered statistically significant.

Results: The mean changes of augmented sockets were between 0.4 mm (2 weeks) and 0.8 mm (12 weeks). In non-augmented sockets changes of 0.7 mm (2 weeks) and of 1.0 mm (12 weeks) were demonstrated. The mean values differed significantly between the buccal and oral region (p < 0.01). Overall, there were significant differences of the mean dimensional changes regarding time (p < 0.01) and augmentation (p < 0.01).

Conclusions: Augmented sockets showed less resorption within 4 weeks after extraction compared to non-augmented sockets. Non-augmented sockets showed a continuous dimensional loss with a great variation over 12 weeks whereas augmented sockets had the highest degree of resorption between 4 and 6 weeks. At 12 weeks a comparable resorption in augmented and non-augmented sockets was observed.

Endodontic and periodontal management of a severely affected maxillary lateral incisor having combined mucosal fenestration and palatogingival groove
Sarang Sharma, Dhirendra Srivastava, Vishal Sood, Priya Yadav

Abstract:
Mucosal fenestrations, wherein the tooth root apices are clinically discernible in the oral cavity subsequent to loss of overlying alveolar bone and mucosa, are rare pathologic entities. Palato gingival grooves—anatomic aberrations—are also infrequent occurrences that notoriously predispose to periodontal pathologies of varying extent. Both conditions independently are known to popularly affect maxillary lateral incisors. Coexistent fenestration defect and palato gingival groove in the same tooth is extremely rare and undoubtedly is a perfect combination to precipitate severe endodontic-periodontal consequences. In this report, a 34-year-old patient presented to the dental department with complaint of esthetics in relation to exposed root of right maxillary lateral incisor. On closer inspection, a palato gingival groove in addition to fenestration defect was evident on the root surface along with aperiosteal pocket of >5 mm. An interdisciplinary treatment was instituted which included endodontic treatment followed by root end resection, osseous bone graft placement and guided tissue regeneration procedures for repair of mucosal fenestration defect. Debridement of the palatal pocket, with saucerization of the groove and restoration with glass ionomer cement were simultaneously employed to correct the palatal defect.