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RESEARCH ARTICLE

LOW BONE MINERAL DENSITY IS ASSOCIATED WITH SMOKING AND BODY MASS INDEX.

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Abstract

Aims: To explore the prevalence of osteoporosis in type 2 diabetic elder males and the risk factors of low bone mineral density in Tibet. **Methods:** 147 Chinese Tibetan older males with type 2 diabetes were recruited from the department of endocrinology of People's Hospital Tibet Autonomous Region. Multiple sites of bone mineral density were measured by dual-energy X-ray absorptiometry.

Results: Among type 2 diabetic males aged 50 years or older who dwelled in high altitude, the percentage of patients with osteoporosis was 12.2%. Body mass index and Smoking were independently associated with BMD T-scores of multiple skeleton sites; Uric acid level was independently associated with T-scores of lumbar spine and total hip.

Discussion: The bone metabolisms should be further investigated in people who dwelled in high altitude since there are big differences of life style and natural environment existed in high landers from people at sea-level in China.

Conclusions: Among type 2 diabetic males aged 50 years or older who dwelled in high altitude, 12.2% patients have osteoporosis. Body mass index and smoking were predictive risk factors for bone mass loss in all skeleton sites. While uric acid level was independently associated with bone mass loss of spine and hip.

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Introduction:-

Due to longer life expectancy and lower physical activity, type 2 diabetes mellitus (T2DM) and osteoporosis have both become significant public health problems. The relationship between T2DM and bone metabolisms has been extensively investigated. Studies on bone mineral density (BMD) in T2DM showed contradictory results with higher, lower or similar values in comparison with non-diabetic subjects. Although patients with T2DM are known to have various changes in the BMD, a growing body of evidence suggested that patients with type 2 diabetes had increased risk for fracture. National Osteoporosis Foundation (NOF) suggested that all men age 50 and older should be evaluated for osteoporosis risk in order to prevent fracture. Many factors including alcohol abuse, excessive

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thinness, high salt intake, genetic diseases, hypogonadal states, endocrine disorders and some medications have been associated with an increased risk of osteoporosis-related fracture.

High-altitude hypoxia may stimulate secretion of many hormones that have affected bone mineral metabolisms. It is well documented that thyroid hormones, cortisol, catecholamines and growth factors increased with altitude (Basu et al., 2013). Increased glucocorticoids are known to inhibit bone growth and cause osteoporosis by inhibiting osteoblast proliferation (Seibel et al., 2013). While increased thyroid hormones is known to stimulate bone resorption more than formation and cause bone mass reduction (Tuchendler and Bolanowski, 2014). It was reported that bone metabolism could be changed during residency at extreme altitude. However, few reports are available on the prevalence of osteoporosis and the predictive factors for osteoporosis for type 2 diabetic highlanders.

This study examined the prevalence of osteoporosis and the determinants of BMD in male individuals ≥ 50 years of age with T2DM dwelling in Tibet. To our best knowledge, this is the first study to report the prevalence of osteoporosis and explore the risk factors of osteoporosis in diabetic males in high altitude.

Materials and Methods:-

Study population:-

The participants were Tibet-dwelling, type 2 diabetic males aged 50 years or older who were admitted to department of endocrinology of People's Hospital of Tibet Autonomous Region for glucose control. The inclusion criteria were as follow: 1) subjects were diagnosed as T2DM in according to WHO 1999 criteria; 2) subjects were native dwellers; 3) aged 50 years or older; 4) Not receiving treatment for osteoporosis or drugs known to affect bone and mineral metabolism. A total of 147 type 2 diabetic males were enrolled in our study. The study was approved by the Institutional ethnic committee of People's Hospital of Tibet Autonomous Region.

Laboratory examinations:-

Histories of duration of diabetes and hypertension were obtained from inpatient medical records. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). All blood samples were obtained at fasting state. Fasting blood glucose (FBG), serum total cholesterol (TC), triglyceride (TG), low- and high-density lipoprotein cholesterol (LDL-C and HDL-C), uric acid (UA), glutamic-oxaloacetic transaminase (ALT), glutamic-pyruvic transaminase (AST) and serum creatinine (CRE) were determined with enzymatic methods on automatic biochemical analyzer (Architech-C1600, USA). HbA1c was measured by high-performance liquid chromatography method (SYSMEX G8, Japan) with reference range from 4.0% to 6.0%. Blood routine examinations were performed by automated hematology analyzer (Sysmex XE-2100, Japan).

Bone mineral density measurements:-

Multiple sites BMD examination was routinely performed by a dual-energy X-ray absorptiometry (DXA) (Hologic Discovery W S/N 86724, Bedford, USA) for each patient with T2DM in our institution. Daily calibration was carried out with a manufacture-provided phantom and the maximum coefficient of variation (CV%) of BMD was 0.1%. Bone density was measured at the lumbar spine (L1-L4) and proximal femur on a postero-anterior scan. BMD was expressed in g/cm^2 and as peak bone mass percentage in normal subjects (T-score), depending on the software used in the device. The reference range of normal subjects in our study was adopted from that in mainland, China. According to WHO criteria and 2015 International Society for Clinical Densitometry (ISCD) official position (Krueger, 2015), osteoporosis was diagnosed in men age 50 and older if the T-score of the lumbar spine, total hip, or femoral neck is -2.5 or less.

Statistical analyses:-

All statistical analysis was performed using SPSS 16.0 (IBM, Inc, New York, USA). Continuous variables were expressed as mean \pm SD. Since duration of T2DM did not follow a normal distribution, the values were Log transferred (eg. Ln duration of DM) and displayed as median and interquartile range. Pearson's correlation analysis was carried out to analyze the relationship between two variables that meets normal distribution. Multiple stepwise linear regression analysis was performed to determine the independent risk factors associated with BMD T-scores.

Results:-

Baseline characteristics of subjects:-

The baseline characteristics of subjects were presented in Table 1. A total 147 male patients were analyzed. The average ages were 59 ± 7 years old with BMI $25.0 \pm 3.3 \text{ kg/m}^2$. The median duration of diabetes was 5 years, and the mean HbA1c was $11.7 \pm 3.0\%$. 39.3% of patients had hypertension and 47.3% was on smoking. The prevalence of osteoporosis and osteopenia was 12.0% and 55.3%, respectively.

Association between baseline characteristics and bone mineral density in multiple sites:-

Pearson correlation analyses were performed to investigate the association between baseline characteristics and BMD T-scores in lumbar spine, femoral neck and hip, respectively (Fig 1). BMI was positively correlated with T-scores of lumbar spine ($r=0.199$, $p=0.015$), femoral neck ($r=0.223$, $p=0.006$) and hip ($r=0.248$, $p=0.002$). Advancing age was only positively correlated with T-scores of lumbar spine ($r=0.187$, $p=0.022$), but not correlated with other sites. Uric acid concentrations were positively correlated with T-scores of lumbar spine ($r=0.207$, $p=0.013$) and hip ($r=0.176$, $p=0.035$). Neither lipid profiles nor glucose metabolisms associated with BMD of all sites.

Predictive risk factors of low bone mineral density in multiple sites:-

Multiple stepwise linear regression analyses were performed to determine the strongest predictors for BMD T-scores at different sites. When BMD T-scores of lumbar spine was entered as dependent variable and age, BMI, duration of diabetes, HbA1c, SBP, UA, CRE, hypertension and smoking as independent variables, the strongest predictors of BMD T-scores of lumbar spine were smoking, BMI and UA (Table 2). When BMD T-scores of femoral neck was entered as dependent variable and age, BMI, duration of diabetes, HbA1c, SBP, UA, CRE, hypertension and smoking as independent variables, the strongest predictors of BMD T-scores of femoral neck were smoking and BMI (Table 3). When BMD T-scores of hip was entered as dependent variable and age, BMI, duration of diabetes, HbA1c, SBP, UA, CRE, hypertension and smoking as independent variables, the strongest predictors of BMD T-scores of hip were smoking, BMI and UA (Table 4).

Discussion;-

In the present retrospective study, we showed that among men age 50 and older with T2DM who dwelled in high altitude, 12.0% patients have osteoporosis, 55.3% patients have osteopenia and 32.7% are normal. Both smoking and BMI were associated with BMD T-scores at multiple sites. Serum uric acid was associated with BMD T-scores at lumbar spine and hip.

The prevalence of osteoporosis varied widely among worldwide populations and few reports on the prevalence of osteoporosis in high altitude are available. A large-scale study showed that osteoporosis affected 3%-6% of men over 50 years old in Europe. In Hong Kong, the prevalence of osteoporosis in men aged 50 years and older was 7.0%. In Taiwan, among men aged ≥ 50 years, average prevalence of osteoporosis was 1.6%. In mainland China, reported overall prevalence of osteoporosis based on nationwide surveys was 22.0% in men over 50 years and older. In our study, the percentage of osteoporosis in type 2 diabetic men aged over 50 years old was 12.0%, which was much higher than most areas.

We found that BMI was positively correlated with BMD T-scores in multiple sites. This finding is consistent with previous studies that showed obesity had a protective effect on BMD. A recent meta-analysis showed that higher BMI is a strong independent factor leading to higher BMD in diabetic population. However, one study showed only visceral adipose tissue, but not subcutaneous adipose tissue was negatively correlated with BMD. And some adipocytokines were reported to be correlated with bone metabolisms. It is known that higher BMI is one of the important factors which determine BMD by increasing mechanical loading and remodeling forces on the bone. Our patients with diabetes had a mean BMI of which is lower than western diabetes (mean BMI 27.8), which probably explained the higher prevalence of osteoporosis in our population than that in western population.

As showed in our study, cigarette has been identified by previous studies as an independent risk factor for low BMD. Longitudinal studies indicated that rates of bone loss were approximately one and a half to two times greater if one is a current smoker (Slemenda et al., 1992). The mechanisms by which smoking might adversely affect bone mass are not known. A 3-year follow up study suggests that impaired calcium absorption in intestinal in cigarette smokers may be one contributing factor (Krall and Dawson-Hughes, 1999). The toxic effects of components of

cigarette on bone collagen synthesis and alterations in metabolism of adrenal cortical and gonadal hormones by smoking were also proposed (Khaw et al., 1988).

We found that serum uric acid levels were independently and positively associated with BMD T-scores in lumbar spine and hip, which was accordance with previous studies. Nabipour et al. first reported that higher UA was correlated with higher BMD at all skeletal sites in men aged 70 years or over. Zhao et al. performed a cross-section study of 621 Chinese men with T2DM and also found that serum UA levels were positively associated with BMD at all sites after adjusting for multiple confounders (Zhao et al., 2016). A large longitudinal study of 16,708 Korean men aged 50 years or older showed that higher serum uric acid played as a protective factor for bone loss during an average follow-up period of 3 years (Kim et al., 2014). Oxidative stress has adverse effects on bone metabolisms. In vitro studies show that reactive oxygen species inhibit the differentiation, proliferation, and activity of osteoblasts by modulating redox-sensitive signaling pathways, whereas they promote bone resorption either by directly stimulating osteoclast differentiation or by indirectly increasing the expression of receptor activator of NF- κ B ligand in osteoblasts. Serum acid is a strong endogenous antioxidant by scavenging free radical, therefore, may protect against metabolic bone diseases such as osteoporosis.

Diabetic-specific parameters did not predict BMD. Some studies but not all showed that diabetic duration, severity and hypoglycemic drugs may affect BMD in older adults with T2DM. The relationships between HbA1c levels and BMD are contradictory. Previous studies using bone turnover markers have suggested that T2DM disease process may have a negative impact on bone. Animal studies showed that increased blood-glucose levels and impaired glycemic control caused by T2DM have been associated with an increased accumulation of advanced glycation end products (AGEs) in bone collagen and impaired calcium deposition and mineralization, which are thought to affect bone strength. However, the effects of glucose metabolisms on bone metabolisms are not proved in human including in our study.

This study has several limitations. First, results from small sample size in a single-center may not be generalized. Therefore, prospective studies with large samples are further needed to verify our results. Second, the cross-sectional retrospective study could not determine a causal relationship between baseline characteristics and BMD T-scores. Finally, there was no control group for individuals at sea level, therefore we could not exclude the effects of high altitude environment on osteoporosis, although studies at sea level have been deeply performed and documented.

Conclusions:-

Among type 2 diabetic males aged 50 years or older who dwelled in high altitude, 12.2% patients have osteoporosis, 55.8% patients have osteopenia and 32.0% are normal. Body mass index and smoking were predictive risk factors for bone mass loss in all skeleton sites. While uric acid level was independently associated with bone mass loss of spine and hip.

Acknowledgment:-

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Conflict of interest;-

All authors have no conflict of interest.

Ethical approval:-

The study was approved by the Institutional ethnic committee of People's Hospital of Tibet Autonomous Region. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For retrospective study formal consent is not required.

Pearson correlation between age, BMI, UA and T-scores of all skeletal sites.

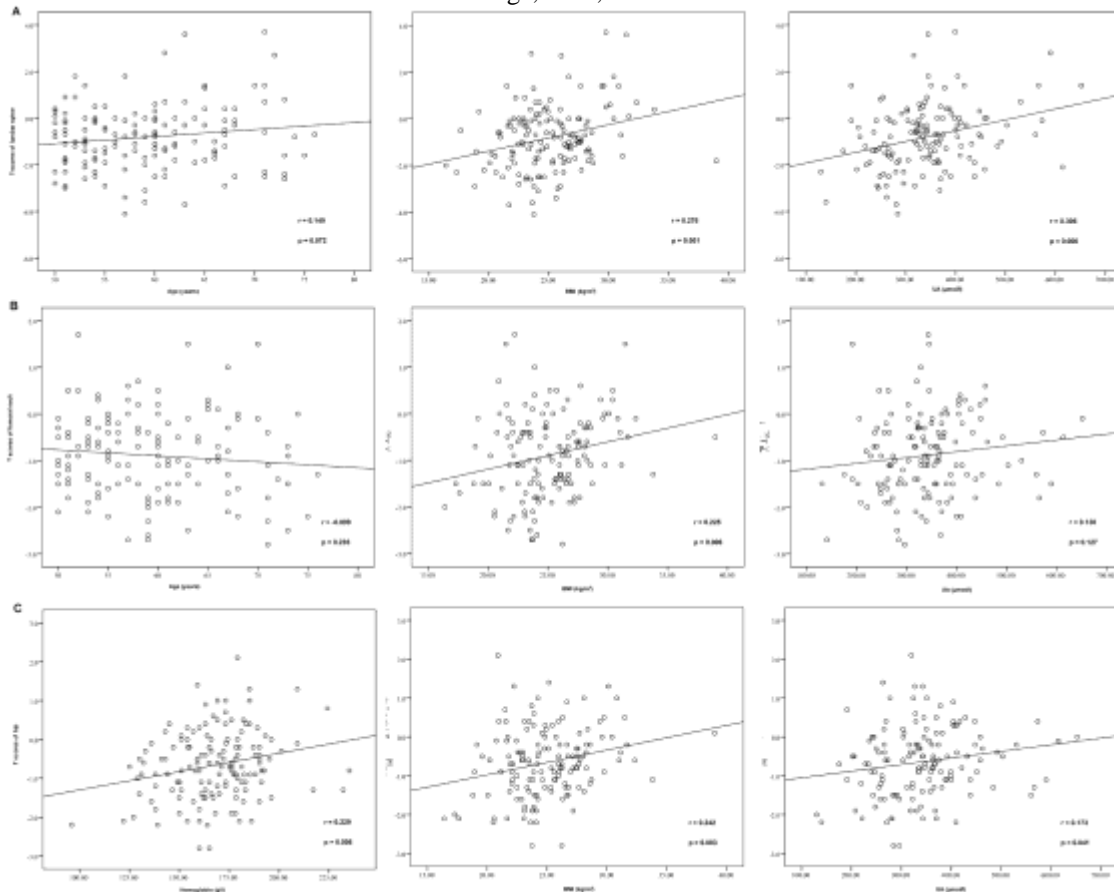


Fig 1:- BMI was positively correlated with T-scores of lumbar spine ($r=0.199$, $p=0.015$), femoral neck ($r=0.223$, $p=0.006$) and hip ($r=0.248$, $p=0.002$). Age was positively correlated with T-scores of lumbar spine ($r=0.187$, $p=0.022$). Uric acid concentrations were positively correlated with T-scores of lumbar spine ($r=0.207$, $p=0.013$) and hip ($r=0.176$, $p=0.035$).

Table 1:-General characteristics of the study patients

Variables	Values
Age (years)	59±7
BMI (kg/m ²)	25.0±3.3
SBP (mmHg)	132±23
DBP (mmHg)	85±14
Duration of DM (years)	5 (1, 10)
Smoking (n, %)	71 (47.3%)
Hypertension (n, %)	59 (39.3%)
HbA1c (%)	11.7±3.0
Hgb (g/l)	168±21
FBG (mmol/l)	10.87±4.34
UA (μmol/l)	341±91
CRE (μmol/l)	67.5±24.3
ALT (U/L)	27 (19, 50)
TC (mmol/l)	4.71±1.22
TG (mmol/l)	1.62±0.89
HDL-C (mmol/l)	1.13±0.28

LDL-C (mmol/l)	2.96±1.02
25(OH)D (ng/ml)	12.7±6.3
BMD	
Normal	47 (32.0%)
Osteopenia	82 (55.8%)
Osteoporosis	18 (12.2%)

BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, DM diabetes mellitus, HbA1c glycated hemoglobin, Hgb hemoglobin, FBG fasting blood glucose, UA uric acid, CRE creatinine, ALT alanine aminotransferase, TC total cholesterol, TG triglyceride, HDL-C high density lipoprotein cholesterol, LDL-C, low density lipoprotein cholesterol, 25(OH)D 25-hydroxyvitamin D, BMD bone mineral density.

Table 2:-Relationship between the baseline characteristics and BMD T-score of spine in multiple linear regression analysis

Variables	B	SE	P	95% CI
Age (years)	0.057	0.020	0.005	0.017 - 0.097
BMI (kg/m ²)	0.098	0.045	0.031	0.009 - 0.187
Duration of DM (years)	-0.035	0.029	0.229	-0.092 - 0.022
Hypertension	-0.226	0.354	0.524	-0.926 - 0.474
Smoking	-0.622	0.291	0.035	-1.199 - -0.045
SBP (mmHg)	-0.003	0.007	0.668	-0.018 - 0.011
Hgb (g/l)	-0.005	0.007	0.451	-0.019 - 0.009
CRE (μmol/l)	0.000	0.007	0.904	-0.014 - 0.013
UA (μmol/l)	0.005	0.002	0.011	0.001 - 0.009
HbA1c (%)	0.065	0.052	0.209	-0.037 - 0.167

BMD bone mineral density, B unstandardized regression coefficient, SE standard error of B, CI confidence interval, BMI body mass index, DM diabetes mellitus, SBP systolic blood pressure, Hgb hemoglobin, CRE creatinine, UA uric acid, HbA1c glycated hemoglobin.

Table 3:- Relationship between the baseline characteristics and BMD T-score of femoral neck in multiple stepwise linear regression analysis

Variables	B	SE	P	95% CI
Constant	-1.912	0.536	0.001	-2.972 - -0.852
Smoking	-0.429	0.140	0.003	-0.707 - -0.151
BMI (kg/m ²)	0.057	0.021	0.008	0.015 - 0.098
Hypertension	-0.390	0.145	0.008	-0.676 - -0.105

BMD bone mineral density, B unstandardized regression coefficient, SE standard error of B, CI confidence interval, BMI body mass index.

Table 4:-Relationship between the baseline characteristics and BMD T-score of hip in multiple stepwise linear regression analysis

Variables	B	SE	P	95% CI
Constant	-3.633	0.762	0.000	-5.141 - -2.125
BMI (kg/m ²)	0.057	0.022	0.010	0.014 - 0.101
Smoking	-0.319	0.144	0.029	-0.604 - -0.034
Hgb (g/l)	0.008	0.003	0.028	0.001 - 0.014
Hypertension	-0.427	0.157	0.007	-0.737 - -0.116
UA (μmol/l)	0.002	0.001	0.043	0.000 - 0.003

BMD bone mineral density, B unstandardized regression coefficient, SE standard error of B, CI confidence interval, BMI body mass index, Hgb hemoglobin, UA uric acid.

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