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Circulating osteocalcin is increased in early-stage diabetes

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ABSTRACT

We aimed to examine whether circulating levels of osteocalcin, bone formation marker secreted from osteoblast, are changed in glucose-intolerant subjects without taking glucose lowering agent, because bone metabolism is reportedly related to glucose metabolism in animal and human studies. According to 75 g oral glucose tolerance test (75 g-OGTT), all subjects (47.6 ± 10.2 years of age; 45 men and 10 women) were divided into three categories: normal glucose tolerance (NGT, $n = 39$), prediabetes (PDM, $n = 11$) that included impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), and diabetes (T2DM, $n = 5$). Serum osteocalcin levels were increased in T2DM as compared to NGT. In all the participants, simple regression analysis model revealed positive correlation of osteocalcin with plasma glucose at 120 min, G(120), on 75 g-OGTT, negative with both creatinine and Ln(CRP), but not significantly with fasting plasma glucose. Osteocalcin and leptin were independent variables for G(120) ($P = 0.026$ and 0.035, respectively). In multinomial logistic analysis leptin (PDM vs. NGT: $P = 0.02$ Odds ratio (OR) of 1.05, 95% confidence intervals, 1.007–1.084) and osteocalcin (T2DM vs. NGT: $P = 0.038$, OR 10.8, 1.13–102.4) were independently associated. We conclude that circulating osteocalcin and leptin are related to glucose intolerant state.

1. Introduction

Bone remodeling is essential to maintain skeleton structure during adult life. Bone resorption and formation, which are mechanistically repairing processes against both micro crack and macro damage, play a pivotal role as bone remodeling. Resorption mediated by osteoclasts differentiated from progenitor cell of bone marrow initiates osteoblast-mediated bone formation after bone destruction at damaged bone and subsequent repair [1,2]. This biphasic process in bone remodeling by these two types of bone cells is normally balanced in healthy individuals. Aging, postmenopausal state and lean body produce imbalance of bone remodeling cycle and consequent osteoporosis with future occurrence of fracture.

Bone is now identified as an organ regulating energy metabolism via osteocalcin that is secreted by osteoblast and enhances insulin secretion in pancreatic islets and insulin sensitivity. Osteocalcin stimulates insulin expression in β-cells, β-cell proliferation and insulin secretion, adiponectin secretion from adipocyte and consequently improvement of insulin sensitivity [3,4]. Osteoblast is regulated via sympathetic nerve that relays energy balance information from adipocyte through hypothalamic leptinergic transmission [1,2,5]. The sympathetic nerve linking to osteoblast uses adrenergic β2 receptor stimulation by two pathways, protein

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kinase A and molecular clock. The former mediates bone resorption by osteoclast stimulation via secretion of RANKL (receptor activation of NF-κB ligand that is released by activated osteoblast) and the latter osteoblast proliferation (bone formation).

In human studies, it was reported that serum osteocalcin concentration is reciprocally correlated with glucose metabolism: osteocalcin is decreased in patients with type 2 diabetes who had never taken hypoglycemic medication as compared to those with normal glucose tolerance [6]. In cross-sectional study, osteocalcin concentration was inversely associated with fasting plasma glucose (FPG), fasting insulin, homeostasis model assessment for insulin resistance (HOMA-R), C-reactive protein (CRP), adipocytokine, BMI and body fat in elderly [7,8]. However, in gestational diabetes patients (GDM), osteocalcin is reportedly greater than normal glucose tolerant pregnant patients and correlated with insulin secretion parameters [9]. Thus, osteocalcin may produce more insulin secretion to overcome insulin resistance as a consequence of pregnancy and weight increase as has been reported in cellular-based study [3–5].

Diabetic patients, who had been taking insulin or oral antidiabetic dugs, exhibited negative correlation of serum osteocalcin with glucose metabolism and fat mass, and positive with adiponectin levels particularly in women [10]. Uncarboxylated osteocalcin is known to be an active form and stimulates the insulin secretion and proliferation of β-cells in studies with animal [3] and human [11]. In diabetic subjects regardless of whether they were treated by glucose-lowering agents, osteocalcin level is associated with improved glucose tolerance [11,12]. Osteocalcin may further mediate both insulin sensitivity and fasting triglycerides, and changes in visceral fat and leg muscle strength are independent variable for serum osteocalcin [13]. These clinical studies suggest that serum osteocalcin is inversely correlated with type 2 diabetes mellitus (T2DM) except for in GDM. Thus, a plausible idea is that in contrast to overt diabetes serum osteocalcin in early-stage diabetes may adaptively be increased to insulin resistance. We evaluated circulating osteocalcin in these subjects with newly found early-stage T2DM or prediabetes including IFG or IGT in annual health check.

2. Materials and methods

2.1. Subjects

We recruited 45 men (mean age of 46.7 ± 7.6 years) and 10 women (55.6 ± 4.6 years) who visited Social Insurance General

Table 1 – Clinical characteristic of subjects.

	NGT (39)	PDM (11)	T2DM (5)	P
Age (years)	47.9 ± 8.2	48.6 ± 8.9	50.6 ± 3.4	NS
Sex (male)	33	9	3	NS
Height (cm)	167.7 ± 7.6	169.9 ± 8.3	162.9 ± 7.6	NS
Weight (kg)	65.9 ± 10.6	75.0 ± 18.1	69.8 ± 11.0	NS
BMI (kg/m^2)	23.3 ± 2.6	26.0 ± 4.8*	26.2 ± 2.7	0.018
Waist (cm)	80.8 ± 7.0	88.5 ± 11.9*	86.4 ± 7.8	0.019
Hip (cm)	93.3 ± 5.2	97.8 ± 8.8	96.9 ± 4.1	NS
W/H ratio	0.87 ± 0.04	0.90 ± 0.04*	0.89 ± 0.05	0.036
SBP (mmHg)	115.1 ± 14.2	124.3 ± 16.1	128.8 ± 26.0	NS
DBP (mmHg)	70.7 ± 11.4	77.2 ± 11.0	79.6 ± 10.9	NS
HbA1c (%)	5.5 ± 0.2	5.7 ± 0.3	6.2 ± 0.4**,##	< 0.001
FPG (mg/dl)	96.3 ± 6.3	105.9 ± 11.6	111.4 ± 11.0	0.016
G(120) (mg/dl)	111 ± 20.0	151.6 ± 23.6**	232.0 ± 22.4**,##	< 0.001
FINS (μU/ml)	8.3 (3.8–13.0)	11.3 (9.6–20.6)	28.9 (4.2–44.0)	NS
Ins(120) (μU/ml)	46.1 ± 29.7	93.6 ± 56.9	163.1 ± 129.1	0.039
HOMA-R	2.10 (0.9–3.4)	3.2 (2.5–4.5)	7.2 (1.2–12.5)	NS
HOMA-β	80.3 (42.0–127.4)	101.9 (75.0–147.0)	192.8 (32.2–348.3)	NS
TC (mg/dl)	194 (176–211)	209 (199–244)	205 (194–233)	NS
TG (mg/dl)	96.0 (75.8–123.0)	111 (83.0–179.0)	129 (74.0–166.5)	NS
HDL-C (mg/dl)	53.0 (47.0–58.0)	55.0 (49.0–56.0)	61.0 (43.5–73.5)	NS
LDL-C (mg/dl)	123 (107–136)	136 (111.4–136)	134 (112–155)	NS
CRP (mg/dl)	0.08 ± 0.14	0.08 ± 0.09	0.14 ± 0.18	NS
Cre (mg/dl)	0.80 ± 0.14	0.75 ± 0.13	0.67 ± 0.19	NS
UN (mg/dl)	14.0 ± 3.2	12.1 ± 3.2	11.5 ± 1.7	NS
Ghrelin (fmol/ml)	14.0 ± 9.3	9.0 ± 4.6	14.8 ± 11.1	NS
LPL (pg/ml)	1.7 ± 0.7	1.9 ± 0.5	1.4 ± 0.3	NS
TNFα (pg/ml)	0.56 (0.48–0.75)	0.63 (0.52–1.10)	0.79 (0.56–1.22)	NS
Adiponectin (ng/ml)	8.5 (5.0–15.9)	7.6 (6.4–17.4)	4.4 (2.3–17.1)	NS
Leptin (pg/ml)	26.0 (13.2–35.0)	46.2 (24.0–65.5)	53.9 (36.7–106.5)	NS
Osteocalcin (ng/ml)	4.1 ± 1.3	4.4 ± 2.1	6.2 ± 1.9*	0.02

PDM included either IFG or IGT, or both. FINS: fasting immunoreactive insulin, I(120): IRI at 120 min during 75 g-OGTT. SBP: systolic blood pressure, DBP: diastolic blood pressure.

* $P < 0.05$ vs. NGT (normal glucose tolerance).

** $P < 0.01$ vs. NGT.

$P < 0.01$ vs. PDM (prediabetes).