Short Communication

Associations between serum bone-specific alkaline phosphatase activity, biochemical parameters, and functional polymorphisms of the tissue-nonspecific alkaline phosphatase gene in a Japanese population

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Introduction: We had demonstrated that single nucleotide polymorphism (787T>C) in the tissue-nonspecific ALP (TNSALP) gene was associated with the bone mineral density (BMD). BMD was the lowest among TNSALP 787T homozygotes (TT-type) and highest among TNSALP 787T>C homozygotes (CC-type) in postmenopausal women. In the present study, we investigated the effects of the TNSALP genotype on associations among serum bone-specific alkaline phosphatase (BAP), serum calcium, and phosphorus in healthy young Japanese subjects. Methods: Young healthy adult subjects (n=193) were genotyped for the polymorphism, and we measured the levels of serum BAP, serum calcium, and phosphorus. Dietary nutrient intakes were calculated based on 3-day food records before the day of blood examinations. Results: Grouped by the TNSALP genotype, a significant negative correlation between serum BAP and phosphorus was observed in 787T>C homozygotes (CC-type), but not in heterozygotes (TC-type), nor in 787T homozygotes (TT-type). Conclusions: In the present study, we revealed that the single nucleotide polymorphism 787T>C in the TNSALP gene had effects on the correlation between serum BAP and phosphorus in young adult subjects. These results suggest that variation in TNSALP may be an important determinant of phosphate metabolism. Our data may be useful for planning strategies to prevent osteoporosis.

Key Words: bone-specific alkaline phosphatase, phosphorus, single nucleotide polymorphism, tissue-nonspecific alkaline phosphatase, young adult subjects

INTRODUCTION

Alkaline phosphatase (ALP; orthophosphoric monoester phospho-hydrolase, alkaline optimum, EC 3.1.3.1.) is classified into two types in most animals, excluding homonidae: tissue-nonspecific (liver/bone/kidney; TNSALP) and intestinal types.[1] In humans, there are at least four types of genetically different isozymes: tissue-nonspecific, intestinal, placental, and germ cell types.[1-3] The *TNSALP gene* is located on chromosome 1 and consists of 12 exons and 11 introns, with the coding sequence beginning in the second exon.[1] TNSALP shows approximately 50% homology with the other three isozymes (intestinal, placental, and germ cell). Their isozymes are tissue-specific and their genes are 90~98% homologous and clustered on chromosome 2.[2,3] The core structures are largely conserved and exhibit the same metal ions and glycosylation sites in all mammalian ALPs. As a result of studies on cDNAs encoding ALP isozymes, it is known that the primary structure in the catalytic region is well conserved in ALPs of humans, animals, and *E. coli.*, suggesting that TNSALP plays an important role in active metabolism by hydrolyzing phospho-compounds, supplying free inorganic phosphate (Pi).

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The physiological roles of ALP are not well understood, but strong evidence is provided by the rare genetic disease hypophosphatasia (HPP). Hypophosphatasia is an inherited disorder characterized by a defect in skeletal mineralization caused by TNSALP deficiency.[4] Various mutations in the *TNSALP gene* have been analyzed.[5-10] Elevated extracellular concentrations of inorganic pyrophosphate (PPi), phosphoethanolamine (PEA), and pyridoxal-5'-phosphate (PLP) have been observed in HPP.[4]

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength, predisposing elderly people to an increased risk of fracture.[11] Osteoporosis results from complex interactions between genetic and environmental factors. Several genes have been implicated as genetic determinants of osteoporosis.[12-13] Recently, we found a significantly higher association between single nucleotide polymorphisms (SNPs) in the *TNSALP gene* (787T>C) (rs3200254 and rs3200255) associated with the bone mineral density (BMD) among 501 postmenopausal women.[14] We genotyped two single nucleotide polymorphisms (787T>C [Tyr246His] and 876A >G [Pro275Pro]), which were shown to be in complete linkage disequilibrium. There was a significant difference in BMD and the BMD score adjusted for age (z-score) among haplotypes, which was the lowest among 787T/876A homozygotes, highest among 787T>C/876A>G homozygotes, and intermediate among heterozygotes. In subgroups divided by age, haplotypes were significantly associated with BMD in older postmenopausal women (>74 years; p=0.001), but not in younger postmenopausal women (≤74 years; p=0.964).[14] These results indicate that the effect of haplotypes on BMD depended on age. Furthermore, these results suggest that variation in TNSALP may be an important determinant of age-related bone loss, and that the phosphate metabolism pathway may provide a novel target for the prevention of osteoporosis.

In the present study, we aimed to clarify the association between serum bone-specific alkaline phosphatase activity and serum biochemical parameters among the TNSALP genotype (787T>C) groups to obtain information for the planning of desirable nutritional management for bone health.

METHODS

The institutional review board of the Japan Women's University approved the protocol, and the study was carried out according to the guidelines of the Declaration of Helsinki. Informed consent was obtained from all the subjects. Participants were excluded if they had metabolic disease. The study population consisted of 97 healthy Japanese males and 96 healthy Japanese females living in Tokyo.[15] All subjects were unrelated volunteers and aged 22.1±1.8 (mean±SD), with a height of 164.9±8.9 cm, weight of 57.2±9.2 kg, and BMI of 21.0±2.3 kg/m^2, respectively.

Fasting blood samples were obtained and sera were kept frozen at -80℃ until measurement. Calcium and phosphorus were measured employing the o-cresolphthalein complexion color development and enzymatic methods, respectively. Alkaline phosphatase activity was determined employing the method of Bessey *et al.*[16] A bone formation marker, bone-specific alkaline phosphatase (BAP), was determined by enzyme immunoassay (DS Pharma Biomedical Co, Ltd, Osaka, Japan). Serum-intact osteocalcin (OC) was measured using an immuno-radiometric assay (Mitsubishi Kagaku Bio Clinical Laboratories Inc, Tokyo, Japan).

All subjects were genotyped for TNSALP polymorphism (Tyr246His, 787T>C) (rs3200254 and rs3200255 were archived in dbSNP at http://www.ncbi.nlm.nih.gov/SNP). Deoxyribonucleic acid was extracted from whole blood (QIAamp DNA Blood kit, Qiagen), and a 219-bp segment of the TNSALP gene including polymorphism sites was amplified by the polymerase chain reaction (PCR).[14] TNSALP polymorphism was determined by direct sequencing using the thermo sequence Cy 5.5 dye terminator cycle sequencing kit (Amersham Biosciences Corp) with a Gene Rapid sequencer (Amersham Biosciences Corp). The amino acid sequence was numbered from the N-terminal of the mature protein, ie, Met at the translation initiation site was –17.[17]

Dietary nutrient intakes were measured based on 3-day food records, taken up to the day before blood examinations. Trained personnel reviewed the food records, and the nutrient content was determined with the use of Eiyo-Kun software (Kenpaku-sha, Japan).

Values are shown as means±SD, and Spearman rank correlation coefficients were calculated to analyze the relation between two parameters. Serum parameters were compared among genotypic categories using ANOVA. Significance was considered at p<0.05. Chi-square tests were conducted to examine whether the genotype frequencies were in Hardy-Weinberg equilibrium. Analysis was conducted using SPSS17.0J (SPSS Inc., USA)

RESULTS

In all subjects (n=193), the mean (±SD) levels of serum BAP and ALP activity were 26.9±7.8 and 192.9±48.0 U/L, respectively. The levels of serum calcium and phosphorus were 9.7±0.4 and 3.6±0.5 mg/dL, respectively. The level of serum osteocalcin was 7.9±3.1 ng/mL. The mean (±SD) dietary intakes of energy, calcium, phosphorus, and vitamin D were 2,078±555 kcal/day, 556±223 mg/day, 1,059±302 mg/day, 5.8±4.8 μg/day, respectively.

The distribution of TNSALP gene polymorphism (Y246H, 787T>C) did not deviate from the Hardy-Weinberg expectations (p>0.05). The allele frequencies were 0.453 for the T allele and 0.547 for the C allele in all subjects. Forty-three subjects showed the 787T (246Tyr, TT-type) homozygote, 89 subjects were heterozygous (TC-type), and 61 subjects showed the 787C (246Tyr, CC-type) homozygote. There was no significant differences among these genotype groups in terms of the height, weight, and serum parameters (ALP, BAP, OC, calcium and phosphorus), as shown in Table 1. There was also no significant differences among these genotype groups in terms of dietary intake: energy, calcium (mg/1,000 kcal/day), phosphorus (mg/1,000 kcal/day), and vitamin D (μg/1,000 kcal/day), as shown in Table 2.

The associations between serum BAP and serum biochemical parameters are shown in Table 3. There was a significant positive correlation between the level of BAP and ALP in all these genotypes. In 787C (246Tyr, CC-type) homozygotes, there was a significant positive corre-

Table 1. Body and serum parameters

	TT (n=43)	TC (n=89)	CC (n=61)	*p*-values
Height (cm)	165.0 ± 10.2	164.6 ± 8.0	165.4 ± 9.2	N.S.
Weight (kg)	57.7 ± 10.3	56.7 ± 8.9	57.7 ± 9.0	N.S.
ALP (U/L)	193.9 ± 56.9	191.2 ± 42.5	194.7 ± 49.3	N.S.
BAP (U/L)	26.6 ± 7.5	26.9 ± 7.0	27.1 ± 9.0	N.S.
OC (ng/mL)	7.7 ± 3.0	7.7 ± 3.1	8.5 ± 3.3	N.S.
Calcium (mg/dL)	9.8 ± 0.4	9.7 ± 0.4	9.8 ± 0.5	N.S.
Phosphorus (mg/dL)	3.6 ± 0.5	3.5 ± 0.5	3.7 ± 0.5	N.S.

Each value represents the mean ± SD.
ALP: alkaline phosphatase; BAP: bone-specific alkaline phosphatase; OC: osteocalcin
N.S.: not significant

Table 2. Dietary intake of energy, calcium, phosphorus, and vitamin D

	TT (n=43)	TC (n=89)	CC (n=61)	*p*-values
Energy (kcal/day)	2,064 ± 567	1,998 ± 506	2,205 ± 600	N.S.
Calcium (mg/1,000 kcal/day)	279 ± 103	265 ± 88	276 ± 95	N.S.
Phosphorus (mg/1,000 kcal/day)	532 ± 90	502 ± 82	518 ± 91	N.S.
Vitamin D (μg/1,000 kcal/day)	3.1 ± 2.8	2.6 ± 1.9	2.9 ± 1.9	N.S.

Each value represents the mean ± SD.
N.S. : not significant

lation between the level of BAP and OC (r=0.502, p<0.001), and there was a significant negative correlation between the levels of serum BAP and phosphorus (r= -0.299, p=0.019) (Table 3). A significant negative correlation between serum BAP and phosphorus was not present in heterozygotes (TC-type), nor in 787T homozygotes (TT-type) (Table 3).

DISCUSSION

This study investigated the contribution of SNPs at the human TNSALP associated with BMD on phosphate metabolism. As shown in Table 3, our study revealed that TNSALP genotypes have an effect on the relationship between serum BAP and phosphorus statuses. Interestingly, a significant negative correlation between serum BAP and phosphorus was observed in 787T>C homozygotes (CC-type), but not in heterozygotes (TC-type), nor 787T homozygotes (TT-type). These results suggest that serum bone-specific ALP activity may be reflected by the level of serum phosphorus differently depending on the TNSALP genotypes. In addition, a significant positive correlation between serum BAP and OC was observed in 787T>C homozygotes (CC-type) and in heterozygotes (TC-type), but not in 787T homozygotes (TT-type) (Table 3). OC is one of the secreted osteoblast-specifc proteins, and both BAP and OC are serum markers of bone-formation. Bone-specific ALP is thought be a more immature osteoblastic marker than OC. Although the reason why serum BAP was associated with serum OC levels in some TNSALP genotypes is unclear, we supposed that the genetic variance may affect the association between serum BAP and OC levels at the differential stage of osteoblasts.

We previously reported that BMD was lowest among 787T homozygotes (TT-type), highest among 787T>C homozygotes (CC-type), and intermediate among heterozygotes (TC-type) among 501 postmenopausal women.[14] The present study demonstrated that TNSALP 787T>C has an effect on, not only age-related bone loss, but also phosphate metabolism in young adult subjects.

The polymorphic 787T>C base change causes an amino acid substitution of histidine for tyrosine at position 246 in TNSALP. There was no significant difference in the levels of ALP-specific activity between 787T and 787T>C using the mouse stromal cell line ST2 cells, derived from mouse bone marrow transiently expressing SNPs of the human TNSALP (787T or 787T>C) gene.[18] However, the expression of the protein translated from 787T>C (His-246) had a lower Km value than 787T (Tyr-246).[18] The Km value indicates the concentration of the substrate at 1/2 Vmax (maximum velocity), and the kinetic affinity for the substrate. The kinetic affinity may affect the mediation of the specificity and modulation of activity, and may contribute to regulatory effects on phosphate

Table 3. Association between the level of serum BAP and serum biochemical parameters

BAP	TT (n=43)		TC (n=89)		CC (n=61)	
	r	*p*-values	*r*	*p*-values	*r*	*p*-values
ALP	0.831	0.000***	0.818	0.000***	0.750	0.000***
OC	0.276	0.073	0.298	0.005**	0.502	0.000***
Calcium	0.008	0.959	-0.008	0.940	-0.098	0.450
Phosphorus	-0.055	0.725	-0.114	0.286	-0.299	0.019*

ALP: alkaline phosphatase; BAP: bone-specific alkaline phosphatase; OC: osteocalcin
* : p<0.05, ** : p<0.01, *** : p<0.001

metabolism. Previously, we reported that Pi starvation increased TNSALP activity and regulated its expression in ST2 cells.[19,20] These results suggest that the possible role of the Pi sensing system in biological functions of ALP might have been evolutionarily conserved.

In mineralizing tissues, the ratio of Pi to PPi, which is an inhibitor of the formation of hydroxyapatite crystals, is important. TNSALP may play a crucial role in the mineralizing process, and may regulate extracellular PPi concentrations by hydrolyzing PPi, which is an inhibitor of the formation of hydroxyapatite crystals.[21] The production of PPi is controlled by the nucleoside triphosphate pyrophosphohydrolase (NTPPPH) isozymes, such as plasma cell membrane glycoprotein-1 (NPP1). Current knowledge of mice lacking TNSALP suggests that TNSALP has essential physiological functions in the metabolism of phospho-compounds.[22] Millán *et al* showed that bone mineralization in double-KO mice lacking both TNSALP and NPP1 is essentially normal, providing evidence that TNSALP and NPP1 are key regulators of the extracellular PPi concentrations required for bone mineralization. [22]

Most recently, a genome-wide association study of the serum phosphate concentration has been reported, and the group reported polymorphisms in seven loci associated with the serum phosphorus concentration.[23] Interestingly, the most robust association in the study was for SNP RS1697421, which is located adjacent to the TNSALP gene.[23] In the present study, TNSALP 787T>C had an effect on the level of serum phosphorus in young adult subjects. As shown in Table 3, we demonstrated the effect of the candidate osteoporosis-susceptibility gene TNSALP on phosphate metabolism, and suggested that the level of bone-specific ALP activity was significantly correlated with serum phophorus in 787T>C, but not in 787T homozygotes. As there are limitations of this association study due to the small sample size, further analysis of bone metabolism including the phosphate metabolism pathway is necessary for the prevention and treatment of osteoporosis, and will help elucidate the molecular and cellular functions of TNSALP.

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AUTHOR DISCLOSURES

None of the authors has any conflict of interest.

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日本族群之血清中骨特異性鹼性磷酸酶活性、生化指標及組織非特異性鹼性磷酸酶基因的功能多型性之相關

前言：在過去的研究中，我們已證實了在組織非特異性鹼性磷酸酶(TNSALP)基因中的單一核苷酸多型性(787T>C)與骨礦物質密度(BMD)有關。在停經婦女中，TNSALP 787T 同型合子(TT 型)者其 BMD 最低；而 787T>C 同型合子(CC 型)者 BMD 則是最高。在本研究中，主要探討健康年輕的日本受試者，其 TNSALP 基因型對於血清中骨特異性鹼性磷酸酶(BAP)、血清鈣與磷相關性的影響。方法：健康青年受試者共 193 位，檢測該基因多型性及測量血清中 BAP、鈣與磷。由抽血檢查前 3 天的食物記錄來估算其膳食營養素攝取情形。結果：依據 TNSALP 的基因型加以分組，發現基因型為同型合子 CC 型者，其血清中 BAP 及磷呈顯著負相關；但在異型合子 TC 型及同型合子 TT 型者身上皆無此相關。結論：在本研究中，顯示了年輕成人受試者，其 TNSALP 基因中的單一核苷酸多型性(787T>C)會影響血清中 BAP 與磷之相關。此結果說明了 TNSALP 的變異可能是影響磷代謝的重要決定因子，而此資料對於預防骨質疏鬆症之防治策略可能是有用的。

關鍵字：骨特異性鹼性磷酸酶、磷、單一核苷酸多型性、組織非特異性鹼性磷酸酶、年輕成人受試者