In a Population Based Association Study IAPP Gene Variants Are Not Associated With Bone Phenotypes in Elderly Women

Adam Mitchell[2,3], Peter Grabowski[2], Kristina Åkesson[1], Fiona E McGuigan[1]

[1]Lund University, Dept of Clinical Sciences Malmö and Skåne University Hospital, Sweden; [2]University of Sheffield, Human Nutrition Unit, Department of Oncology and Metabolism, UK; [3] Uppsala University, Dept of Surgical Sciences, Uppsala, Sweden

Introduction

Osteoporosis is a systemic skeletal disease characterized by reduced bone mineral density (BMD), leading to enhanced bone fragility, and a consequent increase in fracture risk (1). Amylin, also known as Islet Amyloid Polypeptide (IAPP), is co-secreted with insulin from pancreatic B-cells; stimulates bone formation and decreases bone resorption via its action on osteoblasts and osteoclasts (2, 3) and also has the ability to reduce body weight (4, 5). Osteoporosis is a complex, polygenic disorder (6) and the potential for amylin as a candidate gene is highlighted by the large number of diabetics who suffer from osteopenia (7).

Conclusion

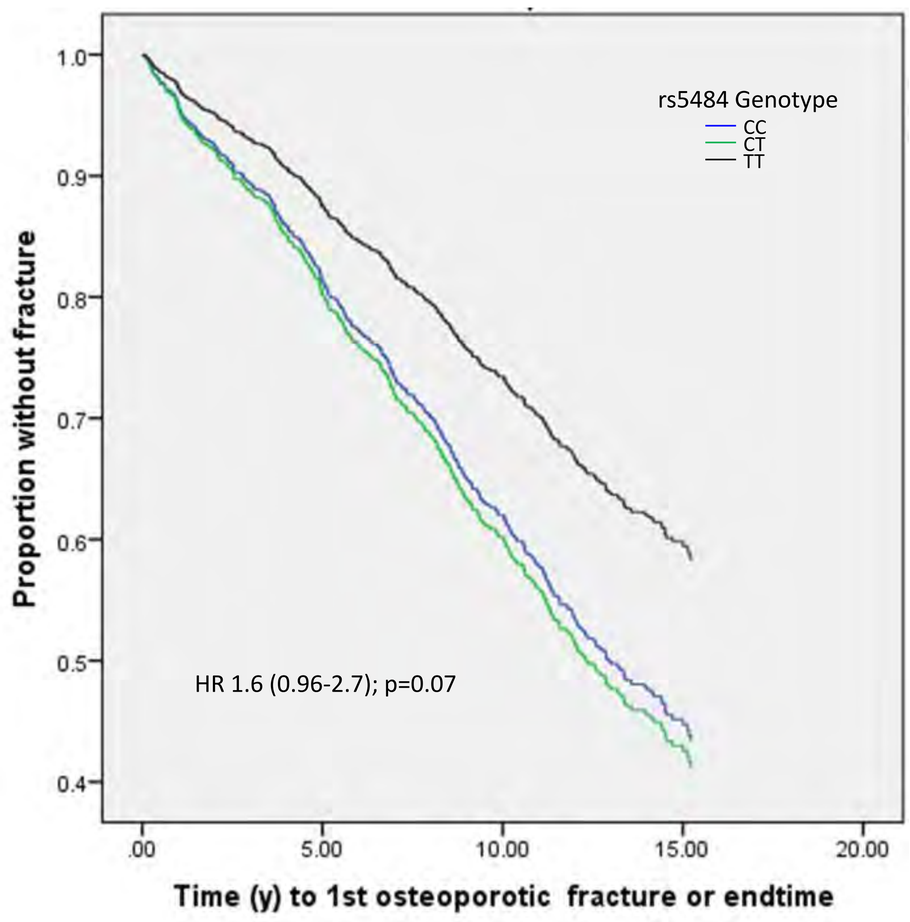
The present prospective data suggest no association between the *IAPP* variants tested and altered BMD in elderly women.

However replication studies are required to fully explore the association of *IAPP* rs5484 and risk of osteoporotic fracture in additional cohorts.

Patients and Methods

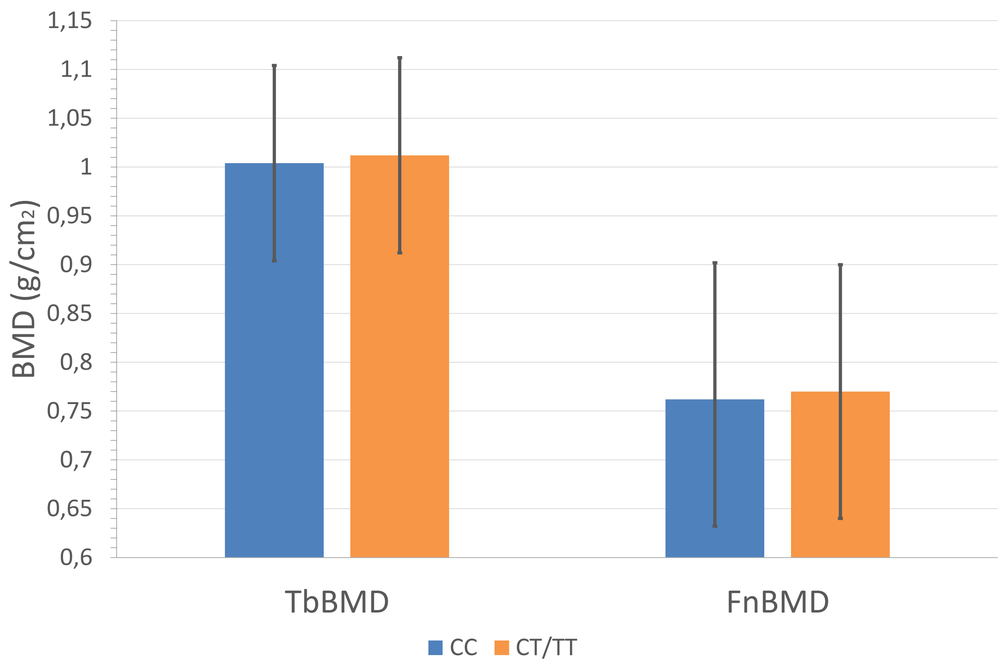
We investigated the association between 4 single nucleotide polymorphisms (SNPs) in the *IAPP* gene and BMD, quantitative ultrasound (QUS) and fracture risk - taking into account body composition- in 75 year old women prospectively followed for up to 15 years (OPRA cohort; n=1003) (8). The association between *IAPP* genotype and BMD and QUS was analysed using a general liner model analysis of variance (GLM-ANOVA). The association between genotype and incident fractures was estimated using binary logistic regression and the association between genotype and incident fractures over 15 years of follow up was determined using a Cox's regression model. All analyses were adjusted for the covariates weight and current smoking status. The OPRA study had >80% power to detect relative risks for fracture of at least 1.2.

Fig. 1 Association between *IAPP* SNP rs5484 and incident osteoporotic fracture over a 15 year follow up



Cox's regression model. Patients are censored after first incident osteoporotic fracture. Osteoporotic fracture sites include hip, vertebra, distal radius, shoulder, and pelvis. Reference category TT: Rare homozygous. CC: common homozygous. CT heterozygous. Analyses adjusted for weight and current smoking status.

Fig. 2 Total body BMD (tbBMD) & femoral neck BMD (fnBMD) by SNP rs5484 genotype



Results are displayed as mean and standard deviation. CC: Women homozygous for the major allele. CT/TT: heterozygotes and women homozygous for minor allele combined.

Table 1. Association of *IAPP* SNP rs5484 and incident fracture in the OPRA cohort

rs5484	Genotype	Without fracture (%)	With fracture (%)	P value	Odds ratio (OR)	95% CI	
						Lower	Upper
Osteoporotic fracture	TT	34 (68)	16 (32)	.17			
	CT	172 (52.6)	155 (47.4)	.06	1.8	.98	3.5
	CC	338 (54.3)	284 (45.7)	.08	1.7	.94	3.2
Any type fracture	TT	29 (58)	21 (42)	.43			
	CT	155 (47.4)	172 (52.6)	.21	1.5	.81	2.7
	CC	311 (50)	311 (50)	.32	1.4	.75	2.4

Reference category (rare homozygote, TT). P-values calculated by binary logistic regression; adjusted for weight and current smoking status. 'Any type' fracture sites include hip, vertebra, distal radius, shoulder, pelvis and proximal tibia fractures. 'Osteoporotic' fracture sites include only hip, vertebra, distal radius, shoulder, and pelvis.

Results

No association was found between any *IAPP* SNP and altered phenotypes of BMD, QUS or body composition.

For *IAPP* rs5484, heterozygous (CT) individuals and those homozygous for the major allele (CC) had a 1.8 and 1.7 times risk respectively of osteoporotic fracture compared to those homozygous for the minor allele (TT), however neither were significant (p=.058 and p=.080).

An increased risk of fracture was also apparent when measured over a 15 year follow-up in those heterozygous (CT) subjects (HR 1.6 (CI: 0.962-2.67), P = 0.07) and homozygous for the major allele (CC) (HR 1.52 (CI: 0.919-2.52), P = 0.10) compared to those homozygous for the minor allele.

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