May the polymorphism of low molecular weight protein tyrosine phosphatase (LMW-PTP/ACP1) modulate metabolic and bone remodelling parameters associated with osteoporosis?

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Introduction

- Osteoporosis is a multifactor disease which interaction between genetic and environmental factors lead to a reduction of bone mineral density accompanied by changes in bone microarchitecture level, leading to a significant decrease in bone strength and an increased fracture risk.
- Acid phosphatase (ACP1) is a cytoplasm enzyme of osteoblast and osteoclast involved in signal transduction associated with regulation of bone metabolism, growth, cell mobility and adhesion.
- It has been demonstrated its importance in bone metabolism verifying an inverse relationship between its expression/activity and those of Src kinase. This, in turn, when increased leads to a decrease in osteoblast differentiation and, consequently, to an imbalance in bone remodeling mechanisms.

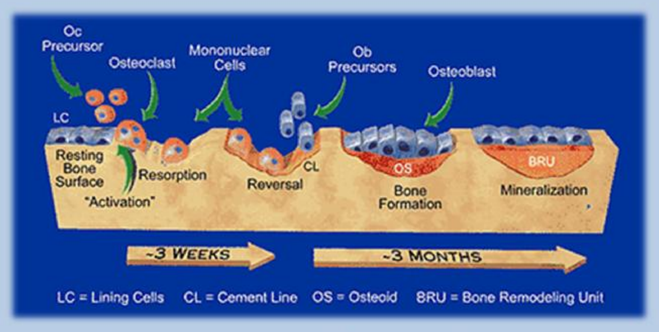

Fig. 1: Bone Remodeling Mechanism

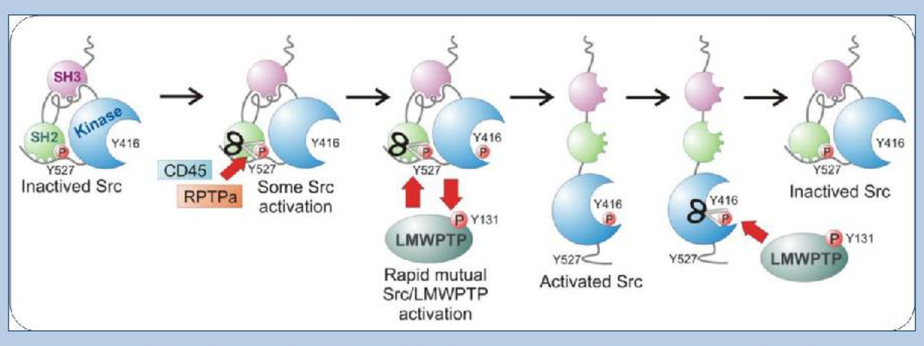

Fig. 2: Src activity modulation by dephosphorylation

- The locus encoding ACP1 is located on the short arm of chromosome 2 (2p25) and contains three most common co-dominant alleles (A, B and C). These give rise to 6 genotypes that result in differences in ACP1 enzyme activity.

Aims

To study the association of protein tyrosine phosphatase (LMW-PTP/ACP1) polymorphism with bone mineral density and metabolic parameters of bone remodelling.

Population

760 subjects:

- 448 normal BMD - (359 Female and 89 Male; 49.7±12.9 years; 30.2±5.4 kg/m²)
- 312 osteoporosis (265 Female and 47 Male; 63.9±10.4 years; 27.16±4.4 kg/m²)

Methods

- BMD (g/cm²) was accessed at the lumbar spine, femoral neck and distal radius, as well as the total body soft tissue composition by DEXA.
- Metabolic bone remodelling parameters were analyzed: LDL, HDL, total cholesterol, triglycerides, $HOMA_{IR}$, alkaline phosphatase (AP) and osteocalcin.
- ACP1 activity was measured by spectrophotometry.
- ACP1 polymorphism was evaluated by PCR.
- Statistical analysis with SPSS 21.0 and Primer of Biostatistics were applied to the results.

Results

1. Association was found between genetic polymorphism of ACP1 and its enzymatic activity with higher values for C allele carriers (AC, BC), intermediate values for BB and lower values for AA and AB.

ACP1 Genotype	ACP1 activity (mean SD; n)		
	Normal BMD + Osteoporosis	Normal BMD	Osteoporosis
AA/AB	280.42 81.99 (90)	270.37 86.36 (39)	288.11 78.47 (51)
BB	305.76 105.02 (57)	302.68 111.52 (36)	311.02 95.24 (21)
AC/BC	419.65 114.12 (21)	414.82 130.41 (7)	422.06 110.31 (14)
p value	**<0,001**	**0,004**	**<0,001**

2. Comparing the metabolic bone remodelling parameters analysed within ACP1 genotypes, for normal BMD and osteoporosis separately, we found association between genotypes BB/BC/AC and: increased ACP1 and decreased alkaline phosphatase in normal BMD and increased $_{t}$cholesterol , LDL and ACP1 in osteoporosis.

Population	Parameter	ACP1 Genotype BB/BC/AC (mean SD; n)	ACP1 Genotype AA/AB (mean SD; n)	p value
Normal BMD	**Acid Phosphatase**	320.94 120.61 (43)	270.37 86.36 (39)	**0.034**
	AP (UI/l)	54.45 14.49 (22)	68.75 19.97 (28)	**0.030**
Osteoporosis	**Acid Phosphatase**	355.43 114.17 (35)	288.11 78.48 (51)	**0.004**
	$_{t}$cholesterol (mg/dl)	232.50 34.31 (40)	216.04 36.29 (42)	**0.033**
	LDL (mg/dl)	152.90 33.30 (40)	138.23 28.86 (48)	**0.029**

3. Comparing the metabolic bone remodelling parameters analysed between normal BMD and osteoporosis we found: increased LDL, $_{t}$cholesterol , alkaline phosphatase, osteocalcin and ACP1 and decreased HOMA in osteoporosis.

Parameter	Normal BMD (mean SD; n)	Osteoporosis (mean SD; n)	p value
$_{t}$cholesterol (mg/dl)	197.15 39.57 (361)	211.47 42.33 (270)	**<0.001**
LDL (mg/dl)	117.35 33.40 (327)	133.72 117.35 (260)	**<0.001**
AP (UI/l)	68.12 22.43 (313)	74.71 34.44 (185)	**0.021**
Osteocalcin (ng/ml)	6.47 5.94 (241)	8.99 11.24 (157)	**0.010**
$HOMA_{IR}$	2.35 2.38 (325)	1.79 1.38 (175)	**<0.001**

4. Studying the correlation between significant metabolic bone remodelling parameters for each population, we found: positive correlation between alkaline phosphatase and osteocalcin and $HOMA_{IR}$ in normal BMD and positive correlation between alkaline phosphatase and LDL, $_{t}$cholesterol and osteocalcin in osteoporosis.

Population	Parameter		Correlation (n)	p value
Normal BMD	**Alkaline Phosphatase (UI/l)**	**Osteocalcin (ng/ml)**	R=0.146 (229)	**0.027**
		$HOMA_{IR}$	R=0.162 (227)	**0.007**
Osteoporosis	**Alkaline Phosphatase (UI/l)**	**$_{t}$cholesterol (mg/dl)**	R=0.169 (131)	**0.032**
		LDL (mg/dl)	R=0.247 (152)	**0.002**
		Osteocalcin (ng/ml)	R=0.286 (148)	**<0.001**

5. Studying the same correlations in each population and for BB/BC/AC and AA/AB individuals, separately, only correlations of alkaline phosphatase with LDL and $_{t}$cholesterol remained significant for AA/AB individuals.

Conclusion

- In osteoporosis, ACP1 polymorphism appears to modulate some metabolic parameters associated with a decrease in BMD, including total cholesterol, LDL and ACP1 activity.

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Calcium, vitamin D and bone
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