CHAPTER 7

CONCLUSIONS

In the current investigation, the separate contributions of waist and hip circumference disease risk were investigated. Based on previous observations demonstrating that a smaller HC, for a given WC, was associated with an increased risk for metabolic disturbances[1-3], type 2 DM[2, 4, 5], and CVD[6, 7], it were examined the independent associations of WC and HC to atherogenic, inflammatory and prothrombotic metabolic syndrome clinical features. The contribution of both thigh adipose and muscle tissue to the referred associations were also studied.

Visceral adiposity has been associated with an unfavourable metabolic syndrome profile and a higher type 2 DM and CVD risk[8, 9]. However, the underlying pathophysiological mechanisms are not totally clear. In addition, it is still unclear if a larger abdominal subcutaneous adipose tissue mass is associated to an increased disease risk, independently of VAT. On the other hand, despite the differences already observed in the associations of metabolic syndrome features with both abdominal and thigh AT compartments, few studies have been addressing the contribution of each AT depot to adipokines secretion, and thus, to its influence in metabolic function. In this sense, it was studied the independent associations of both VAT and Ab SAT compartments to metabolic and disease risk. Additionally, the associations of femoral-gluteal AT with metabolic syndrome features were also investigated.

It is widely accepted that higher circulating FFA levels, commonly present in abdominal obese patients, may promote several metabolism disturbances such as impaired glucose uptake and oxidation in skeletal muscle as well as in several other lean tissues[10]. VAT-derived FFA released into portal circulation drain directly to the liver, promoting liver ectopic fat storage. This liver lipotoxicity may lead, in the first stage, to several metabolic disturbances, including increased dyslipidemia and gluconeogenesis, and a reduction in hepatic insulin clearance[8, 9]. Furthermore, liver fat has been considered a metabolic risk

predictor independently of abdominal and visceral adiposity[11, 12]. Contrarily, recent studies have suggested that this independent liver fat metabolic risk prediction capacity was not present in lean premenopausal women[13]. Based on these observations, it was investigated the independent associations of liver fat with major metabolic syndrome features, and with several other inflammatory and atherothrombotic risk factors.

SUMMARY

The main contributions of the current dissertation are drawn as follows:

- In *Chapter 3*, the protective role of larger HC in IR and dyslipidemia, when WC is taken into account, was extended to specific atherothrombotic metabolic syndrome clinical features.
- The observed counteracting effects in diabetogenic and atherogenic markers were mediated by femoral-gluteal AT.
- Thigh muscle tissue mediated a protective contribution to prothrombotic disturbances.
- Therefore, HC can contribute to additionally predict cardiovascular disease risk in overweight and obese women.

- In *Chapter 4*, VAT and Ab SAT were independently associated with atherothrombotic and inflammatory disturbances, reflecting a higher CVD risk.
- Additionally, VAT was an independent predictor of IR and dyslipidemia markers.
- When controlling for age, BMI and CRF, higher TTAT and TTSAT areas were inversely related with atherogenic risk factors. However, these relations did not

remain significant when controlling for TTMT. A higher TTSFAT area reflected a higher metabolic and CVD risk.

- Our results indicate that thigh lipid pools are related with adipokines, suggesting that they should be also considered as body composition predictors of specific metabolic syndrome features.

- In *Chapter 5*, we found that thigh subfascial AT was inversely associated with liver fat, suggesting a preventive role of this thigh AT depot against hepatic steatosis in overweight and obese women.
- Inflammatory and atherothrombotic metabolic syndrome clinical features were independently associated with liver fat in overweight and obese women.
- Our findings highlight the contribution of higher BMI and VAT, especially if associated with hypertriglyceridemia, hyperinsulinemia, and hypercholesterolemia to the metabolic cascade that mediates liver lipotoxicity.

REFERENCES

1. Snijder MB, Dekker JM, Visser M, et al. Larger thigh and hip circumferences are associated with better glucose tolerance: the Hoorn study. *Obes Res.* Jan 2003;11(1):104-111.

2. Snijder MB, Zimmet PZ, Visser M, Dekker JM, Seidell JC, Shaw JE. Independent and opposite associations of waist and hip circumferences with diabetes, hypertension and dyslipidemia: the AusDiab Study. *Int J Obes Relat Metab Disord.* Mar 2004;28(3):402-409.

3. Snijder MB, Zimmet PZ, Visser M, Dekker JM, Seidell JC, Shaw JE. Independent association of hip circumference with metabolic profile in different ethnic groups. *Obes Res.* 2004;12(9):1370-1374.

4. Snijder MB, Dekker JM, Visser M, et al. Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study. *Am J Clin Nutr.* 2003;77(5):1192-1197.

5. Seidell JC, Han TS, Feskens EJ, Lean ME. Narrow hips and broad waist circumferences independently contribute to increased risk of non-insulin-dependent diabetes mellitus. *J Intern Med.* 1997;242(5):401-406.

6. Lissner L, Bjorkelund C, Heitmann BL, Seidell JC, Bengtsson C. Larger hip circumference independently predicts health and longevity in a Swedish female cohort. *Obes Res.* Oct 2001;9(10):644-646.

7. Heitmann BL, Frederiksen P, Lissner L. Hip circumference and cardiovascular morbidity and mortality in men and women. *Obes Res.* Mar 2004;12(3):482-487.

8. Bjorntorp P. "Portal" adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. *Arteriosclerosis.* 1990;10(4):493-496.

9. Despres JP, Lemieux S, Lamarche B, et al. The insulin resistance-dyslipidemic syndrome: contribution of visceral obesity and therapeutic implications. *Int J Obes Relat Metab Disord.* May 1995;19 Suppl 1:S76-86.

10. Jensen MD, Haymond MW, Rizza RA, Cryer PE, Miles JM. Influence of body fat distribution on free fatty acid metabolism in obesity. *J Clin Invest.* 1989;83:1168-1173.

11. Tiikainen M, Tamminen M, Hakkinen AM. Liver-fat accumulation and insulin resistance in obese women with previous gestational diabetes. *Obes Res.* 2002;10(859-867).

12. Nguyen-Duy TB, Nichaman MZ, Church TS. Visceral fat and liver fat are independent predictors of metabolic risk factors in men. *Am J Physiol Endocrinol Metab.* 2003;284:E1065-E1071.

13. Kuk JL, Nichaman MZ, Church TS, Blair SN, Ross R. Liver fat is not a marker of metabolic risk in lean premenopausal women. *Metabolism.* 2004;53(8):1066-1071.