

CHAPTER 1

INTRODUCTION TO THE STUDY

1.1 Background

During the past twenty years, a remarkable increase in knowledge of the mechanisms regarding the action of insulin, the central hormone in postprandial metabolic regulation, has been witnessed. Interest in cellular and molecular mechanisms in the abnormal action of insulin, is based on and conditioned by a high prevalence of insulin resistance. The fact that insulin resistance holds a key position in the pathogenesis of many diseases has lead to the hypothesis that it is the underlying characteristic of the so called metabolic syndrome (also known as Syndrome X, The Syndrome of Insulin Resistance, Reavens' Syndrome, The Deadly Quartet or The New World Syndrome). The metabolic syndrome is a constellation of metabolic abnormalities all characterized by hyperinsulinaemia and insulin resistance (Reaven, 1988; Kaplan, 1989; Ferrannini *et al.*, 1991; Vague & Raccach, 1992; Zimmet *et al.*, 1997; Haffner, 1997). These abnormalities result in secondary metabolic syndrome features including hyperglycaemia, increased triglycerides in combination with a decrease in high density lipoprotein cholesterol (HDL-C), increased very-low-density lipoprotein cholesterol concentrations (VLDL-C) and hypertension (Reaven, 1988; Zimmet *et al.*, 1997).

The metabolic syndrome is also seen in subjects with a normal glucose tolerance, who are (probably genetic) predisposed for NIDDM (Vague & Raccach, 1992). If this disposition is potentiated by central obesity and an inactive lifestyle, it can influence the development of hypertension and dyslipidaemia. The sum of these abnormalities promotes acceleration of atherosclerosis and frequently manifests in some kind of cardiovascular disease (CVD) which is the most common cause of death in the Westernised world (Haffner, 1997; Zimmet *et al.*, 1997; Walker, 1995; Resnick, 1993; Vague & Raccach, 1992; Haffner *et al.*, 1992a). In addition to a genetic and gender determination and a sedentary lifestyle, other factors in the development of the metabolic syndrome are overnutrition, smoking practices, alcohol consumption, and some antihypertensive drugs (Baillie *et al.*, 1998; Walker, 1995; Hjermann, 1992).

Epidemiological studies confirm that the metabolic syndrome does occur commonly in a number

of ethnic groups including Euripides, Mexican-Americans, Afro-Americans, Asian Indians, Chinese, Australian Aborigines, Polynesians, Micronesians and Japanese subjects (O'Dea, 1991; Minoru Imamura *et al.*, 1995; Humphrey *et al.*, 1995; Zimmet *et al.*, 1997).

There are, however, a number of studies which reported that many black Africans with NIDDM do not have insulin resistance. These studies also reported a lack of a relationship between insulin resistance and blood pressure in obese non-diabetic blacks (Chaiken *et al.*, 1993; Chaiken *et al.*, 1991; Saad *et al.*, 1991). These findings suggest that the metabolic syndrome may have different features in blacks than those observed in whites and other population groups.

Only a few studies on the black population of South Africa in which the problem of the clustering of risk factors of cardiovascular disease is addressed, have been done. Studies on rural and urban African populations in the Free State found that elements for a potential epidemic of atherosclerotic cardiovascular disease are present as well as an alarming increase in NIDDM with urbanization. (Mollentze *et al.*, 1995). Unfortunately, the prevalence of the suggested underlying common factor in the metabolic syndrome, insulin resistance, was not mentioned. A study on urban Africans in Cape Town also showed this alarming increase in the prevalence of NIDDM with urbanization (Levitt *et al.*, 1993). Again, nothing was mentioned concerning insulin resistance. Another study by the same researchers (Levitt, *et al.*, 1999) on a peri-urban coloured community (people with mixed ancestry) in Mamre, has shown some clustering of risk factors associated with insulin resistance.

In an overview by Alexander Walker (Walker, 1995) on the African population in transition, it was pointed out that although obesity occurs very often in especially African women, those who lived in rural areas had a low incidence of hypertension, diabetes and coronary heart disease (CHD). Although these diseases tend to increase with urbanisation (especially NIDDM) the incidence of CHD is still much lower in the South African black population than in the white population, while in the USA African-Americans have higher rates than the respective white population.

1.2 The problem

Coupled to recent political changes, urbanisation is occurring very rapidly in the South African population. Urbanisation is accompanied with the adoption of Western lifestyles (acculturation) and dietary habits also known as the nutrition transition (Gross and Monteiro, 1989). Therefore, malnutrition (especially overnutrition), prevalence of risk factors, morbidity and mortality from chronic diseases of lifestyle are expected to increase (Gross and Monteiro, 1989; Mollentze *et al.*, 1995). Hypertension is already common while CHD is still a rare condition in urban black South Africans (Walker *et al.*, 1991; Steyn *et al.*, 1991; Mollentze *et al.*, 1995). In contrast to the universal recognition of obesity as a risk factor for chronic diseases of lifestyle, Walker *et al.* (1991) described the concept of “healthy obesity” in African women. Investigators have also shown racial differences in the existence of insulin resistance in relationship with NIDDM, CHD and CVD (Saad *et al.*, 1991; Chaiken *et al.*, 1993). The above suggest that there may be unique features in the development of NIDDM, CHD and CVD in Africans. Furthermore, Colagiuri and Brand Miller (1997) have hypothesised that “an insulin resistant genotype evolved to provide survival and reproductive advantages for the cold-climate, large game hunters of the last Ice-Age who consumed a low carbohydrate, high protein diet with periodic starvation. Insulin resistance would have minimised glucose utilisation by muscles thereby facilitating the preferential utilisation of glucose by the brain, foetus and mammary gland. But beginning about 10 000 years ago, following the end of the last Ice-Age and the development of agriculture, dietary carbohydrate increased and the selection pressure for insulin resistance decreased in some groups. Agriculture began in the Middle East and spread throughout Europe long before it was developed elsewhere. Hence the prevalence of the insulin-resistant genotype decreased in Europeans and other groups exposed to a high carbohydrate intake for a sufficiently long period of time. Some geographically isolated groups such as the Pima Indians and Nauruans experienced conditions which further diminished the gene pool diversity and resulted in particularly insulin resistant populations”. To what extent the above is true for the African population, remains to be determined. More information on the presence and characteristics of the metabolic syndrome in Africans may guide policies and programmes for promotion of health, timely intervention and prevention of NIDDM and CVD/CHD in Africans during urbanisation.

1.3 Scientific objectives

The aim of this study was to investigate the existence and development of the metabolic syndrome in the African population.

The first question addressed was whether the metabolic syndrome exists in the African population of the Northwest Province and second, if it does, what the characteristics of the syndrome in this population are.

The hypothesis tested in this study was that despite the concept of “healthy obesity” in African women (Walker *et al.*, 1991) the metabolic syndrome will develop in black South Africans when they adopt Western lifestyles.

To achieve these objectives, a cross-sectional study of African men and women volunteers, recruited from 37 randomly selected sites in the Northwest Province and stratified for age, gender and level of urbanisation, was done from 1996 to 1998. The study is known as the THUSA study. **THUSA** means “help” in Setswana, but is also an acronym for **T**ransition and **H**ealth during **U**rbanisation of **S**outh **A**fricans.

All the subjects known to be fasted for at least eight hours from the THUSA-participants were investigated for hyperinsulinaemia and insulin resistance. In these selected subjects (243 women, 202 men, age range 15 - 65 years) the clustering of risk factors for NIDDM and CHD was also examined. The influence of other lifestyle factors such as levels of urbanisation, the smoking habit, alcohol consumption, overnutrition, socioeconomic background and physical activity, on insulin resistance and the metabolic syndrome was also assessed.

1.4 Enunciation of the study

Chapter 1: **Introduction:** The motivation of the study on the metabolic syndrome as part of the larger THUSA - study, is given in the first chapter.

Chapter 2: **Literature review:** The focus will be on insulin resistance and the clustering of risk factors for the chronic diseases of lifestyle (NIDDM,

CHD, obesity). This will be followed by a very brief discussion on the effects of lifestyle in the development of insulin resistance, and the lifestyle changes expected during urbanisation of South African blacks.

- Chapter 3: **Methods:** The design and methodology of this study will be given.
- Chapter 4: **Results:** The results of the larger THUSA study as well as those of the fasted subjects will be presented in this chapter. The limitations of the study and the influence of urbanisation will be discussed.
- Chapter 5: **Results:** The results on the existence of associations between risk markers for the chronic diseases of lifestyle and insulin sensitivity in this population will be presented and discussed.
- Chapter 6: **Results:** The characteristics of insulin resistance in this population will be presented and discussed.
- Chapter 7: **Results:** The results on the clustering of risk factors for chronic diseases of lifestyle in this population will be presented and discussed. Risk estimations for possible markers in the development of insulin resistance and the metabolic syndrome will be presented.
- Chapter 8: **Conclusions and recommendations:** The results of the study presented in Chapters 4 to 7 will be integrated in the conclusions drawn, and recommendations for possible health intervention programmes will be made.