Pharmacological Study of the Effects of Inhibitors of Renin-Angiotensin System and Grape Seed Extract on Features of the Metabolic Syndrome Developed in Fructose-Fed Rats

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Lobna Elkhadragy

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ACE	Angiotensin converting enzyme
Ang	Angiotensin
ANOVA	Analysis of variance
ARB	Angiotensin-receptor blocker
A_S	Absorbance of standard
A_T	Absorbance of test sample
AT_1	Angiotensin II Type 1
AT_2	Angiotensin II Type 2
ATP	Adenosine triphosphate
CHD	Coronary heart disease
CVD	Cardiovascular disease
DM	Diabetes mellitus
FBG	Fasting blood glucose
FFR	Fructose-fed rats
GLUT-4	Glucose transporter-4
GSE	Grape seed extract
HDL	High-density lipoproteins
HFCS	High-fructose corn syrup
HOMA-BCF	Homeostatic Model Assessment – β-cell function
HOMA-IR	Homeostatic Model Assessment – Insulin Resistance
iNOS	Inducible nitric oxide synthase
LDL	Low-density lipoproteins
MDA	Malondialdehyde
NADPH	Nicotinamide adenine dinucleotide phosphate hydrogenase

NCEP/ATP	National Cholesterol Education Program - Adult Treatment Panel
NEDD	N-(1-naphtyl) ethylenediamine dihydrochloride
NEFA	Non-esterified fatty acids
NHANES	National Health and Nutrition Examination Survey
NO	Nitric oxide
NOx	Total nitrate/nitrite
OLETF	Otsuka Long-Evans Tokushima Fatty
p.o.	Per os
PAI-1	Plasminogen Activator Inhibitor 1
PPAR	Peroxisome proliferator-activated receptor
QUICKI	Quantitative Insulin Sensitivity Check Index
RAS	Renin-angiotensin system
ROS	Reactive oxygen species
SBP	Systolic blood pressure
TBARS	Thiobarbituric acid reactive substances
TG	Triglycerides
USA	United States of America
VCl_3	Vanadium trichloride
VLDL	Very low-density lipoproteins
WHO	World Health Organization

The Metabolic Syndrome

The metabolic syndrome is a pathophysiological entity characterized by a clustering of insulin resistance, hyperinsulinemia, dyslipidemia, hypertension and obesity **(Alberti and Zimmet, 1998)**.

The syndrome was originally described by Reaven in 1988 as the clustering of cardiovascular risk factors like hypertension, glucose intolerance, high triglycerides (TG) and low High-Density Lipoproteins (HDL) concentration and it was called syndrome X **(Reaven, 1988)**. Other names used to describe the syndrome include: the insulin resistance syndrome, Reaven's syndrome and the atherothrombogenic syndrome **(Hjermann, 1992)**. The most popular name used now is the metabolic syndrome **(Eckel *et al*., 2005)**.

Since its initial description, several definitions of the metabolic syndrome have emerged. Several expert groups have developed clinical criteria for diagnosis of the syndrome. All groups agreed on the core components of the metabolic syndrome; including obesity, insulin resistance, dyslipidemia and hypertension. Their criteria were similar in many aspects, however they also revealed fundamental differences in their positioning of the predominant causes of the syndrome **(Pacholczyk *et al*., 2008)**.

The most widely accepted of these definitions were produced by the World Health Organization (WHO), the National Cholesterol Education Program – Third Adult Treatment Panel (NCEP/ATP III) and the International Diabetes Federation.

The first attempt to produce diagnostic clinical criteria for the syndrome was done by a WHO diabetes group in 1998 **(Alberti and Zimmet, 1998)**. They chose to call it the 'metabolic syndrome' because metabolic derangements were the cause of all the components of the syndrome. Another definition was introduced by the NCEP/ATP III of USA **(Grundy *et al*., 2004a)**. In 2005, the International Diabetes Federation experts proposed a universally accepted

diagnostic tool that is easy to use in clinical practice and does not rely on measurements available only in research settings, as clamp studies. Also, it provided race-specific normal values for waist circumference, hence it is applicable to populations around the world so that data from different countries can be compared **(Alberti *et al*., 2005)**.

Table (I): Definitions of the metabolic syndrome

WHO definition
Diabetes, impaired fasting glucose, impaired glucose tolerance or insulin resistance (assessed by clamp studies) and at least two of the following criteria: 1. Central obesity: Waist-to-hip ratio >0.90 in men or >0.85 in women or body mass index > 30 kg/m² 2. Serum TG ≥1.7 mmol/l (150 mg/dl) or HDL cholesterol <0.9 mmol/l (35 mg/dl) in men and <1.0 mmol/l (39 mg/dl) in women 3. Blood pressure ≥140/90 mmHg 4. Urinary albumin excretion rate >20 μg/min or albumin-to-creatinine ratio ≥30 mg/g
NCEP/ATP III definition
Any three or more of the following criteria: 1. Waist circumference >102 cm in men and >88 cm in women 2. Serum TG ≥1.7 mmol/l (150 mg/dl) 3. Blood pressure ≥130/85 mmHg 4. HDL cholesterol <1.0 mmol/l (39 mg/dl) in men and <1.3 mmol/l (50.7 mg/dl) in women 5. Serum glucose ≥6.1 mmol/l (110mg/dl)
International Diabetes Federation definition
Central obesity (defined as waist circumference with ethnicity specific values or body mass index >30 kg/m²) plus two or more of the following four factors: 1. Serum TG ≥1.7 mmol/l (150 mg/dl) 2. HDL cholesterol <1.03 mmol/l (40 mg/dl) in men and <1.29 mmol/l (50 mg/dl) in women 3. Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg 4. Fasting plasma glucose concentration ≥5.6 mmol/l (100 mg/dl)

Prevalence of Metabolic Syndrome

Over the last 20 years, the prevalence of the metabolic syndrome has steadily increased in all populations worldwide **(Procopiou and Philippe, 2005)**.

Several studies were conducted in the United States of America (USA) using data from the National Health and Nutrition Examination Survey (NHANES), a cross-sectional health survey of a nationally representative sample of the civilian USA population. In an analysis of data on 8814 men and women aged 20 years or older from NHANES III (1988-1994), the prevalence of the metabolic syndrome was found to be 23.1% **(Ford *et al*., 2002)**. The study used the definition of the metabolic syndrome developed by the NCEP/ATP III. Later, 1,677 participants from NHANES (1999-2000) were included in the analyses. The prevalence of the metabolic syndrome increased to 26.7% **(Ford *et al*., 2004)**. Between 2003–2006, an analytic sample consisting of 3,423 adults, 20 years of age and over, from the NHANES was studied. Approximately 34% of adults met the criteria for metabolic syndrome **(Ervin, 2009)**.

A very consistent finding in several studies is that the prevalence of the metabolic syndrome is highly age-dependent **(Eckel *et al*., 2005)**. For example, the prevalence of the metabolic syndrome in the USA (NHANES III) increased from 7% in participants aged 20–29 years to 44% and 42% for those aged 60–69 years and at least 70 years, respectively **(Ford *et al*., 2002)**.

To estimate the prevalence of the metabolic syndrome in the Mediterranean region, a multicentre study was done on 4254 subjects recruited from five countries: Algeria, Bulgaria, Egypt, Italy and Greece. The metabolic syndrome was diagnosed by the NCEP/ATP III criteria. The prevalence of metabolic syndrome in the population studied was 27.2% but varied greatly among the centers. It was found to be 20.6% in Egypt **(Thanopoulou *et al*., 2006).**

Clinical Outcomes of Metabolic Syndrome

Cardiovascular disease (CVD) is the primary clinical outcome of the metabolic syndrome **(Alberti and Zimmet, 1998)**. This could be expected, since the individual components of the syndrome have long been known to be major cardiovascular risk factors. Thus when they occur simultaneously, it is logical that adverse outcomes should be more likely.

The increased CVD risk in patients with the syndrome ranged in different studies from 30 to 400%. This wide variation could be due to the population studied, the exact definition of the syndrome used and the length of follow-up **(Kahn *et al*., 2005)**.

Mortality from CVD remains, and is expected to remain, the major cause of death in the world. Globally, an estimated 17.5 million people died from CVD in 2005, representing 30% of all global deaths. The situation is more devastating in low- and middle-income countries, where the prevalence of cardiovascular death has increased dramatically in recent years as a consequence of the widening gap between the propagation of a western diet and lifestyle and the as-yet underpowered medical systems in these countries. Thus, 80% of cardiovascular deaths occur in low- and middle-income countries **(Bohm *et al*., 2010)**.

Most people with the metabolic syndrome have insulin resistance, which increases the risk for type 2 diabetes mellitus (DM). It has been found that the presence of the metabolic syndrome is highly predictive of new-onset DM. When diabetes becomes clinically apparent, CVD risk rises sharply. In addition to CVD and type 2 DM, individuals with metabolic syndrome are susceptible to other conditions; including polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances and some forms of cancer **(Grundy *et al*., 2004a)**.

However, it is still unknown whether the risk of CVD in the metabolic syndrome is greater than the sum of its components or not? Some studies have