Assessment of insulin sensitivity in patients with migraine

Thesis

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ABSTRACT

Background: Insulin resistance and high insulin level could have a pathophysiologic implication in migraine. Moreover, a role for insulin resistance in the comorbidity between migraine and vascular diseases has been suggested**.**

Objective: The main aim was to verify whether migraineurs have abnormalities of the glucose and insulin metabolism. A secondary aim was to search for a correlation between these metabolic indices and headache characteristics.

Patients and methods: 20 non -diabetic, non -obese and normotensive migraineurs and 15 healthy volunteers, age and body mass index (BMI) matched, were included. All patients underwent general, neurological and radiological assessment. After a 12-hour fast and 2-hour after glucose loading, serum glucose and insulin were measured and insulin resistance Homeostasis Model Assessment insulin resistance (HOMA-IR) and McAuley insulin sensitivity indices were calculated for all participants.

Results: A significant difference between patients and control subjects for fasting glucose level (P = 0.011) was detected. A statistically significant positive correlations were found between age of the patients at disease onset and fasting serum insulin (P- value = 0.002), (HOMA-IR index) (P- value = 0.002), triglyceride level (P- value = 0.01) and low density lipoprotein (P- value = 0.03) in addition to inverse correlation between the age at disease onset and McAuley insulin sensitivity index (P- value = 0.001). Other disease characteristics (headache frequency and duration) were not significantly correlated with any of the studied metabolic indices.

Conclusions: Impaired fasting glycaemia may be comorbidity in migraineurs. Patients with higher age at disease onset are more likely to be insulin resistant. The interaction between the two conditions is complex and warrants further studies.

Key words: migraine, serum glucose, insulin, insulin resistance.

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بسم الله الرحمن الرحيم

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LIST OF ABBREVIATIONS

ACE: angiotensin I-converting enzyme

aCL: anticardiolipin antibodies

APOE: apolipoprotein E

APS: antiphospholipid syndrome

BMI: body mass index

CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

CGRP: calcitonin gene-related peptide

CSD: cortical spreading depression

CVD: cardiovascular

ELISA: enzyme-linked immunosorbent assay

FHM: Familial hemiplegic migraine

fMRI: functional MRI

GLUCT4: type 4 glucose receptor

HDL: high density lipoprotein level

HOMA-IR: Homeostasis Model Assessment insulin resistance

hs-CRP: high-sensitivity C-reactive protein

IFG: Impaired fasting glucose

IGT: Impaired glucose tolerance

LDL: low density lipoprotein

LHON: Leber's hereditary optic neuropathy

MA: Migraine with aura

MELASE: mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes

MO: migraine without aura

MRI: magnetic resonance imaging

mtDNA: mitochondrial DNA

MTHFR: methylenetetrahydrofolatereductase

MVP: Mitral valve prolapse

NKA: neurokinin A

NO: nitric oxide

Nord-Trondelag Health Study:HUNT study

OC: oral contraceptive

PACAP: pituitary adenylatecyclase activating peptide

PAG: periaqueductal gray matter

PFO: Patent foramen ovale

rCBF: regional cerebral blood flow

SNP: A single nucleotide polymorphism

SP: substance P

SPECT: single-photon emission computed tomography

TNF: tumor necrosis factor

VIP: vasoactive intestinal polypeptide

WMH: white matter hyperintensities

WML: white matter lesions

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INTRODUCTION AND AIM OF WORK

INTRODUCTION

Migraine is a common neurological disorder affecting between 10 and 20% of the population **(Haut et al., 2006)**, and has a complex inheritance **(Honkasalo et al., 1995; Estevez and Gardne, 2004)**. Thepathphysiologyof migraine is complex and involving both the metabolicandneuro-vascular mechanisms**(Hamed, 2009)**. Associations between migraine and vascular disorders such as coronary heart disease and stroke have been reported in previous studies, in addition tosubclinical ischemic brain lesions**(Tietjen, 2007)**.The relationship between migraine and stroke is complex. Cerebral ischemia can induce a migraine-like headache but at the same time ischemic stroke can occur during a migraine attack (**Del Zottoet al., 2008)**.Migraine is increasingly being recognized as an independent risk factor for occurrence of ischemic stroke outside the setting of the migraine episode (**Etminanet al., 2005)**.

Many theories have been postulated to explain the comorbidity between migraine and stroke. It is still unclear whether migraine and stroke are comorbid due to a shared underlying pathogenesis or that migraine itself increases the risk of stroke. One of this supposed shared pathogenesis is the metabolic syndrome. The metabolic syndrome is an established risk factor

for cerebrovascular disease **(Mottillo et al., 2010).**Insulin resistance is a chief component of metabolic syndrome, which occurs when normal level of insulin doesn't produce the same effect on muscle and adipose cells resulting in hyperglycemia and compensatory hyperinsulinemia. Insulin resistance can progress to type-2 diabetes when the β-cells fail to produce sufficient insulin to maintain normal blood glucose level **(McGarry, 2002)**. **Guldiken et al. (2009)** estimated that the 1-year Migraine prevalence was 11.9% in men and 22.5% in women with metabolic syndrome in comparison to 5% to 5.7% in men and 12% to 17.7% in women in a population based study in western countries (**Stewart et al., 1992; Macgregor et al., 2003; Lipton et al., 2007).**

In the last decade,the idea that glucose metabolism throughout the body is coordinated by the brain has gained growing support (**Cavestro et al., 2007)**. insulin is a hormone which thought to influence brain metabolism and cerebral blood flow through insulin receptors, which are found in many parts of the brain **(Schwartz et al., 1992; Porte et al., 2005)**. Furthermore, there is growing evidence that alternations in the insulin and glucose metabolism may beinvolved in the pathogenesis of migraine (**Cavestroet al., 2007). Rainero et al. (2005)**noticed that insulin resistance, whichis considered a risk factor for hypertension **(Lind et al., 1995)**and stroke

(Kernan et al., 2002), is more common in patients with migraine.Moreover, migraine is a disease with diversity of comorbid disorders, including diabetes mellitus **(Aamodt et al., 2007)**. It has long been understood that blood sugar can have an impact on migraine disease; indeed the most frequent triggering factor reported by migraineursis fasting, and migraine is more likely in susceptible persons when there is low insulin receptor activation **(Masters et al., 1986; Rose, 1986).**Moreover, genetic association has been found between migraine and insulin.Five single-nucleotide polymorphisms have been identified within the insulin receptor, significantly associated with migraine **(McCarthy et al., 2001)**.