ORAL GLUCOSE TOLERANCE TEST AND INSULIN RESISTANCE (THE HOMEOSTASIS MODEL ASSESSMENT) IN RELATION TO CATARACT

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Syventävien opintojen kirjallinen työ

Tampereen yliopisto

Lääketieteen yksikkö

Savitaipale study

toukokuu 2012

TAMPEREEN YLIOPISTO

Lääketieteen yksikkö

PENTTILÄ, VILLE: Oraalinen glukoosirasitustesti ja insuliiniresistenssi (HOMA) suhteessa kaihiin

Syventävien opintojen kirjallinen työ, 11 s.

Lääketiede

Toukokuu 2012

Avainsanat: diabetes, metabolinen oireyhtymä, riskitekijät, silmäsairaudet, väestötutkimus

Kaihi on yleisin syy heikentyneeseen näkökykyyn koko maailmassa. Kaihileikkausten aiheuttamat kulut kattavat suurimman osan yhteenlasketuista silmätautien kustannuksista Suomessa. Kaihille on monia riskitekijöitä. Tärkeimmät riskitekijät ovat ikä ja diabetes. Kaihin vallitsevuus Suomessa kasvaa merkittävästi iän myötä, yli 85-vuotialla prevalenssi on 67 prosenttia. Muita riskitekijöitä ovat alhainen sosioekonominen status, tupakointi, geneettiset tekijät, silmätapaturmat, lääkitys (mm. kortikosteroidit), oksidatiivinen stressi ja UV-säteily. Myös metabolinen oireyhtymä ja sen osatekijät ovat yhteydessä kaihiin.

Tutkimuksen tarkoituksena oli selvittää insuliiniresistenssin ja muiden riskitekijöiden yhteyttä kaihiin. Tutkimuksessa verratiin terveitä henkilöitä kaihia sairastaviin ja kaihileikkauksen läpikäyneisiin henkilöihin. HOMA (the homeostatic model assesment) on menetelmä, joka kuvaa insuliiniresistenssiä ja haiman beetasolujen toimintaa. Tutkimus perustui savitaipalelaisiin vuosina 1933-1956 syntyneisiin henkilöihin, joista tehtiin kymmenen vuoden seurantatutkimus. Tutkimuksen alussa ja lopussa henkilöt suorittivat oraalisen glukoosirasitustestin ja täyttivät kyselylomakkeen, jossa kysyttiin terveyttä, elämäntapaa, sosioekonomista statusta ja fyysistä aktiivisuutta koskevia kysymyksiä. Tutkimushenkilöiltä otettiin laboratiokokeita ja mitattiin verenpaine, pituus, paino ja verenpaine. Henkilöistä otettiin seurantavaiheen lopussa silmänpohjan valokuvat sekä retroilluminaatiokuvat, joista eri silmäsairaudet diagnosoitiin.

Tutkimuksen tuloksena insuliiniresistessiä kuvaava arvo, HOMA-IR, nousi kymmenen vuoden aikana enemmän kaihiryhmässä verrattuna terveiden ryhmään. Alkuvaiheessa ryhmien välisessä HOMA-IR-arvoissa ei ollut eroa (p=0,586). Seurantavaiheessa HOMA-IR-arvot olivat 1,51 (terveiden ryhmä) ja 1,90 (kaihiryhmä) (p=0,003). Muissa kliinisissä tekijöissä ei ollut merkittävää eroa.
Tämä tutkimus osoittaa, että insuliiniresistenssi saattaa olla itsenäinen riskitekijä kaihille.

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1 Introduction

Cataracts are an important cause of low vision in both developed and developing countries. The cataract operations cover 57% of total costs of the main four eye diseases in Finland in 2003 [1].

There are many risk factors for cataracts. The main cataract risk factors are age and diabetes mellitus [2]. In Finland the prevalence of cataract increases significantly with age, to 67% in those aged 85 or older [3]. Also low socioeconomic status and smoking are associated with higher frequency of cataract [4]. Other risk factors include the use of corticosteroids, genetic factors, eye injury, oxidative stress and long-term exposure to ultraviolet light or to radiation [5-8].

The metabolic syndrome, its components, and their combination are associated with cataract [9, 10]. According to the International Diabetes Federation the metabolic syndrome components are: waist circumference (≥94cm in men and ≥80cm in women) plus two criteria among raised triglyceride levels, reduced high-density lipoprotein cholesterol levels, raised blood pressure, and raised plasma glucose levels and or/diagnosis of type 2 diabetes. The insulin resistance has not been studied as an independent risk factor of cataract.

The purpose of this study was to determine the homeostasis model assessment (HOMA) and other risk factor differences between patients who had or have had a cataract and patients who did not have a cataract. The HOMA model is used to yield an estimate of insulin sensitivity and beta-cell function from fasting plasma insulin and glucose concentrations. The HOMA modeling is useful when assessing longitudinal changes in insulin resistance. The HOMA insulin resistance model was used for example in the present study that showed decrease in HOMA-IR with combined metformin and fenofibrate therapy in obese patients with hyperinsulinaemia who had not yet developed diabetes mellitus [11]. The HOMA modeling has been described more specifically elsewhere [12].

This study was a 10-year follow-up, population-based study focusing on the metabolic factors of the patients. At the follow-up was the ophthalmic photography of the patients performed.

The insulin resistance plays a role on hypertension independently from obesity and fat distribution across weight classes [13]. In the Brazilian Metabolic Syndrome Study (BRAMS) the cut-off value for insulin resistance was HOMA2-IR > 1.8; and, for metabolic syndrome was HOMA2-IR > 1.4 in non-diabetic suspects [14]. HOMA-IR is an independent predictor of cardiovascular disease in type 2 diabetes [15]. In nondiabetic adults, insulin resistance was associated with risk of incident ischemic stroke [16]. Insulin resistance may be a marker of Alzheimer's disease risk and slight cognitive impairments in adults with prediabetes or type 2 diabetes.

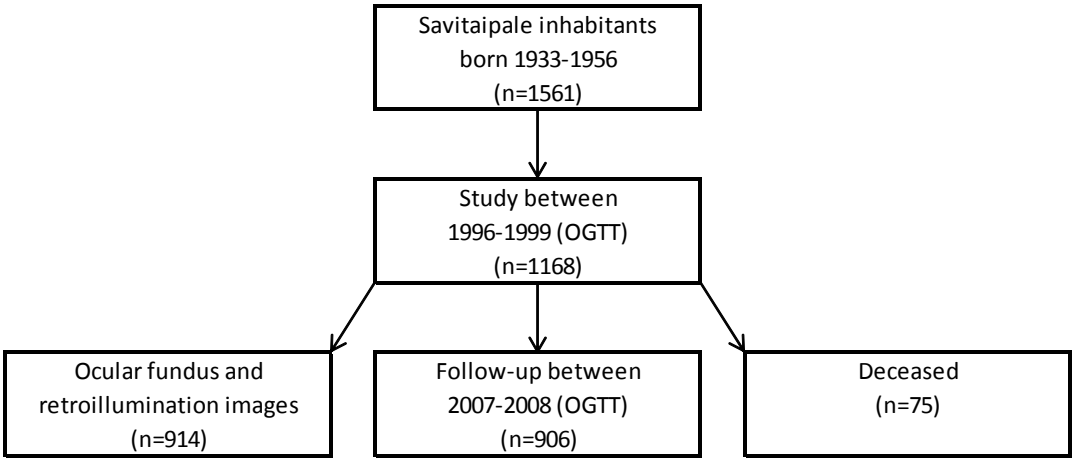
The pathogenesis of cataracts is multifactorial. Three molecular mechanisms are involved in the development of diabetic cataract: nonenzymatic glycation of eye lens proteins, oxidative stress, and activated polyol pathway in glucose disposition [17]. The activated polyol pathway causes an excess of sorbitol in the lens, which leads to swelling of the lens. Oxidative stress is implicated as a cause of insulin resistance and diabetes. And on the other hand obesity and insulin resistance are associated with elevated oxidative damage. [18] Oxidative stress could participate in the formation of cataracts [19].

2 Materials and Methods

2.1 Material

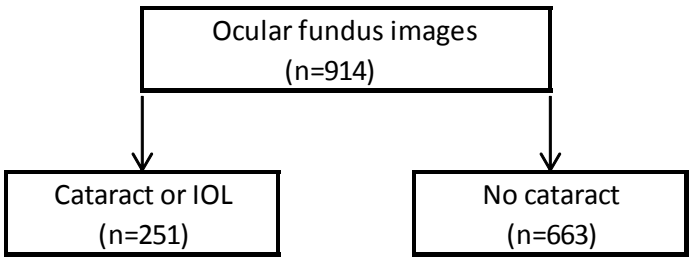
The Savitaipale population-based study was approved by the Ethics Committee of the Hospital District of South Karelia. This study was established to determine changes in glucose tolerance status over a ten-year follow-up. Inhabitants born 1933-1956 were invited to the study between 1996-1999 of whom 1168 underwent an OGTT. The study included a physician interview, physiological measurements (weight, height, blood pressure, and ankle brachial pressure index) and laboratory tests. The subjects were also asked to complete self-administered questionnaires (including MOS-SF36, Beck depression inventory test) concerning health, lifestyle, socio-economic status, physical activity and sleep.

Follow-up took place between 2007-2008. In the follow-up 906 patients underwent an OGTT and laboratory tests. 75 patients were deceased before the follow-up.



2.2 Ophthalmic photography

Ocular fundus and retroillumination images were taken of 914 patients in the follow-up examination. The images were taken with a fundus camera designed to take pictures of the eye fundus. Both papilla and macula centered fundus images were taken. Patients' pupils were dilated using a mydriatic eye drop, tropicamide. The images were stored in the JPEG format and were analysed by two researchers. Borderline cases were analysed together to reach a consensus on the images. The VF-14 questionnaire was used to assess visual functioning and quality of life according to vision.



2.3 Biochemical analysis

The OGTT was measured by a standardized method (WHO 1999). The examination began in the morning between 8.00 hours and 10.00 hours on the study day by taken the intravenous blood sample after an overnight fast of 12 hours.

Plasma glucose was measured by a glucose-dehydrogenase method with a B-Glucose analyser hemicue®-analyzer which was calibrated every morning. Serum insulin was determined by a ABBOTT Laboratories AxSYM® system test in a Public Health Laboratory of Oulu.

Serum cholesterol (FS-Kol, mmol / l), serum HDL-cholesterol (HDL-C, mmol / l) and serum triglycerides (FS-TG, mmol / l) were established in South Karelia General Hospital by an enzymatic colorimetric method (CHOD / PAP), either by Cobas Integra 700- or 400-Integra analyser.

Beta cell function and insulin sensitivity were estimated by the Homeostatic model assessment (HOMA) method from fasting glucose (mmol/l) and insulin concentrations (mU/l). HOMA values were calculated by using an equation described elsewhere (Use and Abuse of HOMA Modeling*).

2.4. Statistical analysis

The data were analyzed with SPSS statistics program. Differences in variables among the groups were analyzed by one way ANOVA. The relations between the characteristics were examined by multiple regression analysis. Data are presented as mean ± SD unless otherwise stated. The statistical significance level was set at 0.05.

3 Results

The study population was divided in two groups; patients who did not have cataract and patients who had a cataract or a cataract surgery (intraocular lens) in either or both eyes. Clinical characteristics of patients are shown in Table 1. The mean age difference between the two groups

were 5.4 years (p=0,000). The mean systolic blood pressure differed between the two groups (p=0,045). Bmi, diastolic blood pressure (DBP), hdl, ldl, triglyceride and VF-14 did not differ between the two groups. The both groups include patients with and without the type 2 diabetes mellitus.

Insulin resistance (HOMA2-IR) increased more in the cataract group during the 10-year follow-up. There were no statistical difference in the HOMA2-IR baseline measurement (p=0,586). At the follow-up the HOMA2-IR values were 1,51 (no cataract) and 1,90 (cataract or IOL) (p=0,003).
There were no statistically significant differences in baseline or follow-up fasting glucose levels (p=0,356 and p=0,167). During the 10-year follow-up, the insulin levels rose in both groups, but showed a difference between the two groups only in the follow-up measurement (p=0,001). The baseline insulin levels were 8,320 mU/l and 8,639 mU/l respectively.

HOMA2-IR Beta cell function explained better the change in the insulin resistance during the 10-year follow-up comparing to HOMA2-IR Insulin sensitivity. HOMA2-IR Beta cell function was different in two groups in follow-up (p=0,008), not in baseline (p=0,212). HOMA2-IR Insulin sensitivity was not statistically significant different in follow-up 90,43 and 82,30 (p=0,056) nor in baseline 129,30 and 117,89 (p=0,08).

In multiple regression analyses age (p=0,000) and HOMA2-IR2 (p=0,004) were independently related to cataract (Table 2). Systolic blood pressure (p=0,626) or bmi (p=0,430) were not independently related to cataract. The multiple regression analysis indicates that insulin resistance is an independent factor of the cataract, despite the differences in the age and systolic blood pressure between the two groups.

Table 1 Clinical characteristics of patients

Characteristic	No Cataract	Cataract/IOL	p value
Age	60,7 (6,2) n=648	66,1 (5,9) n=224	0,000
Bmi	26,2 (4,2) n=645	26,8 (4,4) n=224	0,087
SBP	133,5 (20,5) n=646	136,7 (19,5) n=222	0,045
DBP	84,2 (12,1) n=646	83,7 (11,1) n=222	0,565
Kol	5,57 (0,94) n=645	5,77 (1,11) n=223	0,007
Hdl	1,47 (0,37) n=643	1,50 (0,39) n=221	0,179
Ldl	3,53 (0,86) n=633	3,69 (0,96) n=217	0,230
Triglyceride	1,30 (0,81) n=644	1,33 (0,81) n=223	0,600
HOMA2-IR-baseline	1,08 (0,91) n=597	1,12 (0,69) n=171	0,586
HOMA2-IR-followup	1,51 (1,06) n=616	1,897 (2,58) n=194	0,003
VF-14	94,8 (10,6) n=429	93,2 (14,4) n=123	0,174
T2D baseline	2,93 % n=19	3,60 % n=6	0,529
T2D followup	9,57 % n=62	11,61 % n=26	0,226
Baseline fasting glucose	4,786 (0,6735) n=640	4,737 (0,6417) n=210	0,356
Followup fasting glucose	5,76 (1,09) n=630	5,89 (1,33) n=211	0,167
Baseline-HOMA2-IR Beta cell	109,08 (54,465) n=597	114,78 (45,541) n=171	0,212
Baseline-HOMA2-IR Sensitivity	129,30 (77,802) n= 597	117,89 (64,813) n=171	0,08
Baseline insulin	8,320 (7,6110) n=601	8,639 (5,3321) n=174	0,606
Followup insulin	11,177 (8,147) n=636	15,675 (31,337) n=224	0,001
Followup-HOMA2-IR Beta cell	93,54 (39,209) n=616	111,20 (148,886) n=194	0,008
Followup-HOMA2-IR Sensitivity	90,43 (52,546) n=616	82,30 (48,709) n=194	0,056

Table 2 Regression analyses

Parameter	B	t	Beta	p value
Birth year	-,023	-10,104	-,347	,000
Followup HOMA2-IR	,028	2,877	,102	,004
Bmi	-,003	-,789	-,029	,430
Sbp	,000	-,487	-,018	,626

4 Discussion

This study indicates that the development of the insulin resistance may be associated with cataract. There is a significant difference between the two studied groups, but the multiple regression analysis indicates that the HOMA-IR is independently related to cataract. It might be reasonable to assume that prediabetic changes can be associated in the earlier development of the cataract.

Rates of diabetes have increased markedly over the last decades. The development of type 2 diabetes is well-known and caused by a combination of lifestyle and genetic factors. Type 2 diabetes is due to insulin resistance primarily and lowered insulin production from the beta cells. It is also important to notice pre-diabetic conditions: impaired glucose tolerance (IGT), and/or impaired fasting glucose (IFG). There is a strong link between abnormal glucose metabolism and state of health. The prevention of diabetes and pre-diabetic changes can be achieved with screening and proper nutrition combined with regular exercise.

There are many ways to reduce insulin levels, increase insulin sensitivity, reverse insulin resistance, help reduce insulin, and decrease blood sugar levels without and/or with the use of medication. Weight reduction after successful lifestyle intervention results in improvements of blood inflammatory markers including HOMA-IR [20]. Pairing aerobic activity with individual cognitive behavioral therapy can be used to achieve multiple benefits in diabetic patients [21]. The balance in glucose metabolism depends also highly on diet. A high consumption of sugar-sweetened beverages increases the risk of type 2 diabetes, whereas a high dietary fibre intake,

mainly from whole-grain products, reduces the risk type 2 diabetes [22]. In a Finnish study The dietary pattern rich in fruits and vegetables, was associated with a reduced risk of type 2 diabetes and in contrast, the pattern, which was rich in butter, potatoes, red meat, and whole milk, was associated with a higher risk of type 2 diabetes [23]. Dietary protein intake has also beneficial effect on metabolic factors [24]. For example the consumption of BCAAs predicts improvement in HOMA-IR independent of the amount of weight lost [25]. The improvement of insulin resistance might have beneficial effects not only on glucose control but also on CVD in patients with type 2 diabetes [15].

Abnormal glucose metabolism can be treated with different medications increasing insulin sensitivity and/or augmenting beta cell function [26]. The treatment of the prediabetic patients can reverse prediabetes to normal glucose tolerance [27].

To prevent cataract the most effective strategy would be a healthy life style, but diabetic patients don't have precise information about diabetes ocular changes [28].

Determining of the exact insulin concentration may a weakness in this study, because insulin secretion is pulsatile. Insulin concentrations oscillate at a periodicity of 5-15 min per oscillation. As well there can be bias in every laboratory test taken from the subjects. However the laboratory has been using calibrated and standardized methods to get comparable results.

This study compared the differences in the whole population, and did not focus on any subgroup, for example patients with IGT or IFG. The future studies are needed to examine this population in different subgroups.

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