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ORIGINAL ARTICLE

Metabolic Disorders in Patients With Impaired Glucose Tolerance, With or Without Underlying Ischaemic Heart Disease

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Abstract

Background/Aim: The evidence showed that in the development of diabetes mellitus type 2 (DMT2) and coronary heart disease (CHD) significant role is played by metabolic risk factors: insulin resistance (IR), dyslipidaemia and obesity. Beside metabolic factors, increase in inflammatory markers such as fibrinogen and hs-C reactive protein (hsCRP) plays a role in developing CHD. Metabolic disorders are thought to also be present in patients with impaired glucose tolerance (IGT) and could contribute to development of CHD in these individuals. Aim of this study was to investigate the behaviour of metabolic parameters and chronic inflammation markers in patients with IGT on glucose tolerance test and associated CHD.

Methods: The trial included 4 groups of 30 subjects: a) IGT with CHD, b) IGT without CHD, c) CHD without IGT and d) control group without CHD and with normal glucose tolerance (NGT). Within each group glucoregulation parameters were measured (fasting glucose and Hb1Ac). Oral glucose tolerance test (OGTT) with 75 g glucose load was performed and IR parameters calculated (using HOMA-IR, Matsuda index, Quicki index, HOMA1- %B), lipid profile was done, waist/hip ratio was measured, as well as fibrinogen and hsCRP. CHD diagnosis was determined by typical signs of previous myocardial infarction on ECG, echocardiogram and/or ergometry (Bruce protocol).

Results: Subjects with IGT, but no CHD and those with both IGT and CHD had statistically significantly higher triglyceride and cholesterol levels and manifest IR with decreased insulin sensitivity compared to subjects with CHD, but no IGT and control group. Group with both IGT and CHD was found to have significantly higher fibrinogen and hsCRP concentrations.

Conclusion: IR and hyperlipidaemia, together with chronic inflammation mediators, are potential predictors of the development of glucose tolerance disorders; hence interventional treatment during IGT period or during hyperinsulinaemia could give patients better opportunity to prevent or postpone onset or development of diabetes and its complications.

Key words: Impaired glucose tolerance; Insulin resistance; Coronary heart disease; Chronic inflammation mediators.

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Introduction

The best evidence on increased risk of developing CVD was obtained in DECODE study[1] which showed that impaired glucose tolerance (IGT) was significant predictor of coronary heart dis-

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ease (CHD) mortality. Numerous studies have confirmed that the risk of CHD is significantly higher in diabetics compared to individuals without glucoregulation disorders.[2-7] In manifestation of CHD in patients with diabetes mellitus type 2 (DMT2) indisputable role is played by inflammation mediators, as well as metabolic risk factors complementary to them. Hyperinsulinaemia can have direct atherogenic effect on the blood vessel wall,[7-9] but its atherogenic effect can also be realised indirectly through lipid disorders,[7, 10-12] fibrinolysis[13, 14] and obesity.[15]

Within these studies there is a particular interest in elucidating the effect of insulin levels on severity and progression of CHD as a late DMT2 complication. Decrease in insulin sensitivity is an early sign of susceptibility to diabetes type 2 and it usually manifests as elevated fasting insulin levels.[2] Insulin is a key glucose metabolism regulator that promotes glucose uptake into peripheral tissues and inhibits glucose production in the liver. Insufficient insulin action results in increased levels of fasting glucose and ultimately in overt DMT2.[16-18] Insulin resistance (IR) is also associated with development of cardiometabolic complications, a risk that arises even before development of DMT2.[19, 20] Development of CHD was observed in individuals with IGT without overt clinical or subjective DMT2 signs, therefore current and future research faces a challenge of identifying and preventing potential risk factors for development of CHD in those individuals. Oral glucose tolerance test (OGTT) assesses an individual's ability to clear circulating glucose after a 75 g oral glucose load, after an overnight fast. OGTT induces transition from fasting to feeding and subsequent changes in various metabolic nutrients happen while the body adjusts in order to achieve glucose homeostasis.[21] WHO recommends OGTT as a diagnostic test in the range of fasting plasma glucose between 5.5 and 11.1 mmol/L. Majority of studies conducted in Europe, which compared the ADA and WHO diagnostic criteria, have found that of individuals with DM diagnosed using ADA criteria only 46 % had 2 h glucose concentration higher than 11.1 mmol/L, which indicates that WHO 2 h glucose criterion is more reliable diagnostic test for DM diagnosis.[22]

Aim of this study was to investigate characteristics of metabolic parameters and chronic inflammation markers in individuals with IGT, with and without CHD.

Methods

The study included 120 individuals, ages 45 to 70, divided in 4 groups of 30 subjects: 1st group IGT with CHD, 2nd group IGT without CHD, 3rd group CHD without IGT and 4th group healthy subjects (control group without CHD and with normal glucose tolerance – NGT). The study was conducted at the Department of Endocrinology with General Internal Medicine and at the Clinic of Cardiovascular Diseases of University Clinical Centre in Banja Luka. Patient sample was available to researchers and at the same time it was statistically representative in order for the study to achieve sufficient power. All subjects were informed about the scheduled study and their informed consent was obtained. In accordance with ethical principles inclusion criteria were based on risk factors for impaired glucose metabolism (body mass index ≥ 25, DMT2 in first-degree relatives, middle or older age, history of lipid profile disorder, fasting glucose from 5.0 to 6.5 mmol/L) and on the evidence of CHD, including signs of ischaemia or previous myocardial infarction (IM) on ECG, echocardiogram and/or ergometry.

Exclusion criteria included existing diagnosis of diabetes mellitus, chronic kidney disease requiring dialysis, pregnancy, use of medication or presence of an existing condition that could affect glucoregulation, as well refusal to participate in the study. In each subject following parameters were measured:

- Glucoregulation (fasting glucose, HbA1c);
- OGGT was performed with 75 g oral glucose load after a 12 h fast and glucose and insulin levels were measured at 0 (initial fasting levels, right before taking glucose), 30, 60, 90 and 120 min;
- Parameters of IR were calculated using Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), Matsuda index, Quantitative Insulin Sensitivity Index (QUICKI index), insulinogenic index, HOMA1- %B, lipid profile, waist-to-hip ratio, fibrinogen and CRP;
- Blood pressure and anthropometric measures were taken (waist-to-hip ratio (W/H), Body Mass Index (BMI)).

Apart from OGTT, all the other metabolic parameters were included in the routine patient evaluation during hospitalisation. IGT was determined based on glucose levels between 7.8 and 11.1 mmol/L after 75 g oral glucose load during

OGTT or based on fasting glucose levels of ≥ 6.1 mmol/L and < 7.0 mmol/L. Fasting serum glucose levels were measured using enzyme glucose oxidase method (Biosen C line analyser and Chronolab photometer, CHL-1310). HbA1c levels were measured from haemolysed whole blood samples processed on COBAS INTEGRA 400 plus analyser using turbidimetric inhibition immunoassay (TINIA). Insulin was measured by radioimmunoassay method using INEP RIA INSULIN (PEG) kit. Intra assay coefficient of variation (CVI) was 3.84 %. HOMA index was calculated using this formula: HOMA-IR = (FPI x FPG) / 22.5 (FPI = Fasting Plasma Insulin, FPG = Fasting Plasma Glucose).

Insulin secretion capacity was estimated using insulinogenic index, based on the increase in insulin and glucose levels at 30 min using the following formula: ▲I30/▲G30, where ▲I30 is the difference in insulin levels (mmol/L) at 30 and at 0 min and ▲G30 is the difference in glucose levels (mmol/L) at 30 and at 0 min of the test. QUICKI = 1/[log(I0) + log(G0)], where I0 represents fasting insulin level and G0 fasting glucose level. Matsuda index ISI (Matsuda) = 10000/√ (glucose concentration 0' × insulin concentration 0' × glucose concentration OGTTx × insulin concentration OGTTx), where glucose concentration 0' represents glucose concentration at 0 min (mg/dL), insulin concentration 0' - insulin concentration at 0 min (mIU/L), glucose concentration OGTTx – mean glucose concentration during OGTT (mg/L) and insulin concentration OGTTx – mean insulin concentration during OGGT (mIU/L). Beta cell basal insulin secretion indicator HOMA1- %B = (20 × FPI)/(FPG - 3.5).

For total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol measurement chromatography was used on Roche/Hitachi 917 analyser. CHD diagnosis was made by cardiologist and based on typical findings of previous myocardial infarction on ECG, echocardiogram and/or Bruce protocol ergometry. Statistical data analysis was performed using the Statistica StatSoft program. Results were expressed as mean ± standard deviation. For statistical analysis, Student t-test, Chi-square test, correlation coefficient, uni- and multivariate logistic regression, one-factor and two-factor analyses of variance or Kruskal-Wallis test were used.

Results

Clinical characteristics of patients and biochemical, ie, metabolic parameters are shown in Table 1 and 2.

OGTT was performed on all the subjects and highly statistically relevant difference ($p < 0.01$) was always observed across the groups (Figure 1). At 0 min glucose concentration was approximately the same in the first two groups and was significantly higher compared to the last two groups, whereas in groups 3 and 4 there was no significant difference. At 30 min the highest glucose level (up to 13 mmol/L) was observed in group 2, then in group 1, while in groups 3 and 4 levels were almost the same. Trend towards increase in glucose level at 60 and 90 min was observed in group 1, while decrease in glucose concentration at 120 min compared to at 30 min was observed across all groups. Glucose levels did not return to normal values in the first two groups (9.0 mmol/L in the 1st group and 8.30 mmol/L in the 2nd group), while in the 3rd and 4th group glucose levels did return to values within reference range.

Aside from glucose levels OGTT insulin levels were also measured and highly statistically significant difference among groups ($p < 0.01$) was observed at 0 min and at 120 min, while at 30, 60 and 90 min there was no statistically significant difference ($p > 0.05$) (Figure 2). At 0 min the highest concentration was reported in IGT with CHD group. In the IGT without CHD group insulin concentration was 6 times higher at 30 min compared to fasting level and only at 120 min there was a slight decrease in serum insulin level. In contrast to the control group and the CHD without IGT group where significant steep decline in insulin concentration was observed after the initial increase, it was noted that in IGT with CHD group no decrease was observed, on the contrary, further increase in serum insulin concentration was observed compared to fasting insulin levels.

HOMA-IR index was calculated to determine IR and it showed higher values in subjects with IGT both with and without CHD compared to subjects with normal glucose tolerance and those with CHD, but no IGT, in the statistically significant range (Figure 3).

Table 1: Clinical characteristics of patients

Caracteristics (n = 120)	**IGT with IHD** (n = 30)	**IGT without IHD** (n = 30)	**IHD without IGT** (n = 30)	**Healthy** (n = 30)
Gender (M/W)	20/10	18/12	17/13	14/16
Age	68.50 ± 7.6	57.50 ± 9.76	58.00 ± 10.91	47.00 ± 6.90
BMI (kg/m²)	26.60 ± 4.52	28.69 ± 4.24	25.06 ± 4.12	23.03 ± 4.68
W/H	0.92 ± 0.09	0.97 ± 0.09	0.91 ± 0.10	0.82 ± 0.13
SBP (mm Hg)	145 ± 17.98	140 ± 16.05	145 ± 18.72	120 ± 13.29
DBP (mm Hg)	90 ± 10.31	87.50 ± 10.08	90.00 ± 9.35	80.00 ±7.03
Tobacco (yes/no)	20/10	13/17	21/9	8/22

IGT: impaired glucose tolerance; IHD: ischaemic heart disease; BMI: body mass index: W/H: waist to hip ratio; SPB: systolic blood pressure; DBP: diastolic blood pressure;

Table 2: Patients' metabolic parameters

Caracteristics (n = 120)	**IGT with IHD** (n = 30)	**IGT without IHD** (n = 30)	**IHD without IGT** (n = 30)	**Healthy** (n = 30)
Fasting glucose (mmol/L)	6.30 ± 0.58	5.90 ± 0.59	5.00 ± 0.80	4.45 ± 0.52
HgA1C (%)	5.00 ± 0.89	5.40 ± 0.88	4.00 ± 0.73	3.50 ± 0.91
Glucose 0 min (mmol/L)	6.30 ± 0.86	6.15 ± 0.90	4.70 ± 0.83	4.85 ± 0.91
Glucose in 120 min (mmol/L)	9.00 ± 1.65	8.30 ± 1.65	4.20 ± 1.28	4.05 ± 1.20
Insulin 0 min (pmol/L)	13.78 ± 8.75	8.75 ± 24.91	12.96 ± 11.80	1.29 ± 6.33
Insulin in 120 min (pmol/L)	86.97 ± 57.74	57.74 ± 144	29.37 ± 31.82	28.94 ± 37.00
HOMA indeks	4.22 ± 2.46	7.02 ± 6.36	3.20 ± 2.66	2.72 ± 1.37
HOMA1 - % B	268.57 ± 355.00	283.81 ± 446.21	197.56 ± 420.00	110.32 ± 106.98
QUICKI indeks	0.31	0.32	0.34	0.34
Matsuda index	3.21	3.29	4.88	5.40
Holesterol (mmol/L)	5.20 ± 1.38	5.78 ± 2.05	5.75 ± 1.24	5.50 ± 0.87

IGT: impaired glucose tolerance; IHD: ischaemic heart disease;

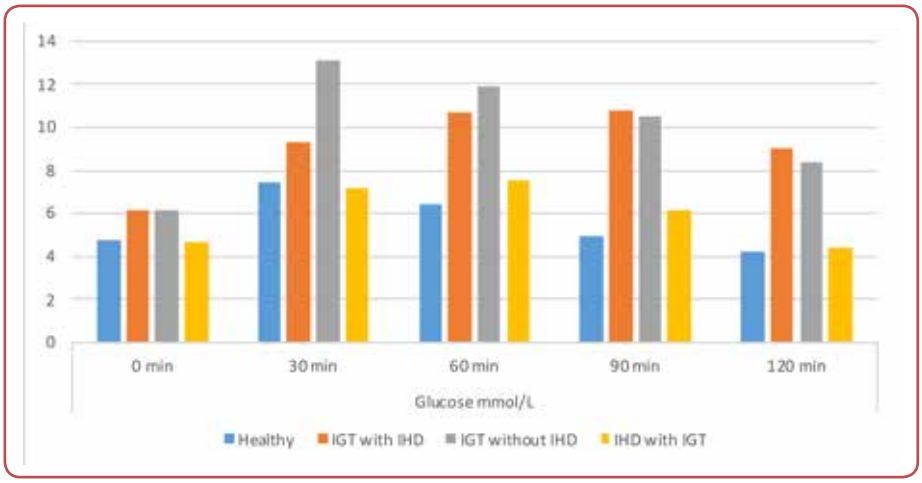

Figure 1: Glucose concentration during OGTT across study groups

IGT: impaired glucose tolerance; IHD: ischaemic heart disease; OGTT: oral glucose tolerance test;

Analysis of QUICKI index values showed that mean values across groups of patients of different status were quite similar. However, ANOVA results suggest that there was a statistically significant difference between values ($F(3) = 3.50$, $p < 0.05$). Review of the results of LSD, post hoc test, revealed that QUICKI index values in the IGT without CHD group were significantly lower on average compared to control and the CHD without IGT group. It was observed that MATSUDA index values were on average the highest in the control group, slightly lower in the CHD without IGT group and the lowest in the IGT without and IGT with CHD groups and statistically significant difference ($F(3) = 2.74$, $p < 0.05$) was recorded between the mean values.

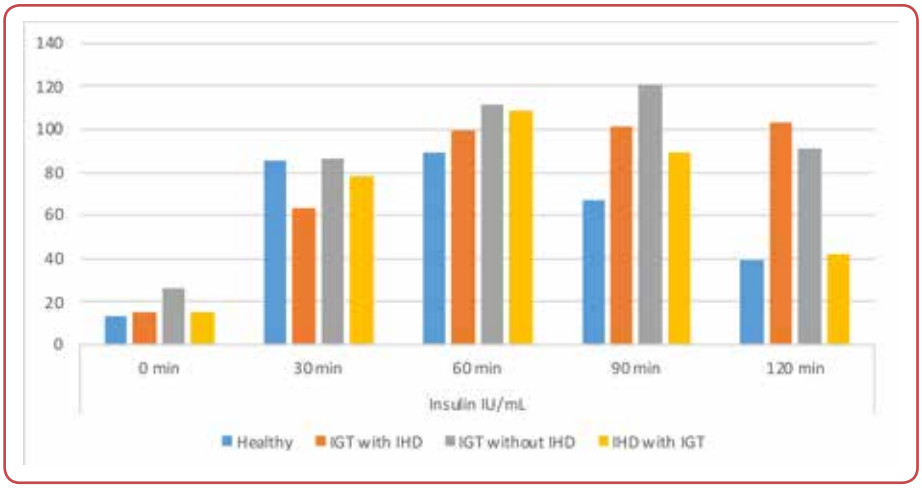

Figure 2: Insulin concentration during OGTT across study groups

IGT: impaired glucose tolerance; IHD: ischaemic heart disease; OGTT: oral glucose tolerance test;

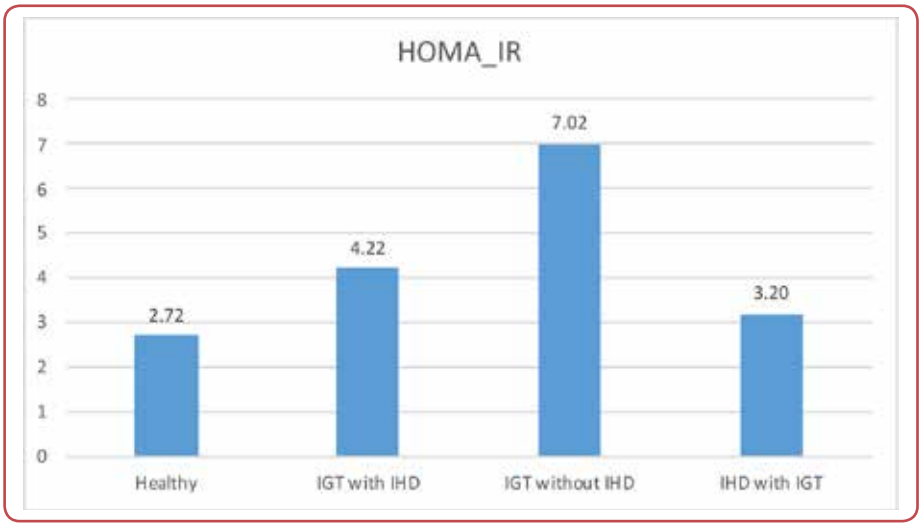

Figure 3: HOMA index of insulin resistance across study groups

IGT: impaired glucose tolerance; IHD: ischaemic heart disease;

Table 3: Levels of hsCRP across study groups

Category	N	M	SD	F	Df	P
IGT with CHD	30	4.82	1.47	133.62	3	.000**
IGT without CHD	30	0.91	0.42			
CHD without IGT	30	1.95	0.88			
Healthy	30	0.68	0.37			

***statistically significant at the p < 0.01 level*
hsCRP: high sensitive C-reactive protein; IGT: impaired glucose tolerance; IHD: ischaemic heart disease; N: number of patients; M: mean; SD: standard deviation; F: f-value, analysis of variance; Df: degrees of freedom; p: p-value;

Table 4: Levels of fibrinogen across study groups

Category	N	M	SD	F	Df	P
IGT with CHD	30	4.93	1.31	47.72	3	.000**
IGT without CHD	30	3.13	0.99			
CHD without IGT	30	3.83	0.96			
Healthy	30	1.85	0.76			

***statistically significant at the p < 0.01 level*
IGT: impaired glucose tolerance; IHD: ischaemic heart disease; N: number of patients; M: mean; SD: standard deviation; F: f-value, analysis of variance; Df: degrees of freedom; p: p-value;

Analysis of the lipid profiles across the groups showed the highest total cholesterol and LDL cholesterol in the IGT with and without CHD groups, although there was no statistically significant difference ($p > 0.05$) between the groups. The highest triglyceride levels were recorded in the CHD without IGT group and the highest mean HDL cholesterol levels in the control group. In subjects with marked postprandial hyperglycaemia, elevated levels of triglycerides and cholesterol and significant hyperinsulinaemia were also observed. In subjects with the highest IR HDL cholesterol levels were the lowest. Triglyceride levels were not the highest in the IGT groups with the highest IR, but in the CHD without IGT groups with normal peripheral sensitivity to insulin, therefore no cause-and-effect relationship with IR was observed in those subjects.

The habit of smoking as the risk factor for CHD was noted in the highest percentage of subjects in the CHD groups with or without IGT, whereas in the group of healthy subjects the habit of smoking was observed in low percentage.

Statistical significance of the differences between CRP and fibrinogen levels across all four study groups was investigated using ANOVA, as is shown in Tables 3 and 4. It was noted that the mean values of CRP and fibrinogen in the IGT with CHD group were markedly higher than in the other groups and were, on average, the lowest in the healthy group.

Discussion

Several researchers suggest that IR is present even before blood glucose abnormalities are detected in patients with diabetes[23, 24] and that hyperinsulinaemia develops before pathophysiological abnormalities associated with IGT. Hyperinsulinaemia is harmful in individuals with normal and abnormal glucose tolerance. Helsinki Policemen Study,[25] Busselton Study,[26] Wisconsin Epidemiologic Study[27] and RISC study[28] have shown that high plasma insulin levels, fasting or after OGTT, are associated with increased risk of major cardiovascular events independent of the other conventional cardiovascular risk factors (including blood glucose, cholesterol, triglycerides, blood pressure, obesity, smoking and physical activity). Study results show that patients in prediabetes state (IGT, IFG – impaired fasting glucose) are at higher risk of CHD. Data from routine preventive exams show that blood glucose concentration, even levels below DM threshold, are associated with coronary artery disease.[29-31] IFG category was introduced to mark the range between the upper threshold of normal FPG and the lower threshold of diabetes FPG. IFG represents an intermediate state of abnormal glucose regulation and is a risk factor for future development of diabetes and CHD.[32]

In 2003 ADA recommended changing the lower threshold for IFG diagnosis from 6.1 to 5.6 mmol/L.[33] As Dankner et al[24] found basal hyperinsulinaemia in normoglycaemic adults is an independent risk factor for metabolic worsening of dysglycaemia in adulthood and may help identify seemingly healthy individuals at increased risk of diabetes. A large number of studies have confirmed the correlation between this metabolic state, decreased insulin sensitivity and resulting IR and development of CVD and the significance of OGTT as a diagnostic method for recruiting these individuals from the general population, in order to timely detect and prevent DMT2.[34-36]

Study results presented in this paper are comparable to other studies. In individuals with IGT, with or without associated CHD, IR index was significantly higher. In healthy controls HOMA index was slightly higher compared to individuals with CHD, which could be explained by BMI in the severe obesity range in a couple of individuals who had normal blood glucose and plasma lipoprotein concentrations and normal blood pressure readings. Individuals with IGT, with or without associated CHD, have impaired insulin sensitivity, significant impairment of beta cell function, manifest hyperinsulinism and the process of pancreatic beta cell apoptosis has probably started. Increased postprandial glucose levels are accompanied by increase in insulin secretion in pancreatic beta cells, but insulin secretion in groups 2 and 1 does not follow the increase in glucose concentrations, that is, the 1st phase of insulin secretion is delayed compared to the last two groups, particularly to the group of healthy individuals where insulin secretion significantly increases and follows the increase in postprandial hyperglycaemia in linear fashion.

Low QUICKI values are a good predictor of diabetes development in adults.[37, 38] In this study this predictive factor was noted in subjects with IGT without and with CHD. In clinical practice, all kinds of simple insulin sensitivity indices are used for the assessment of IR, which has been done in this study as well. Matsuda index is dependent on the accuracy of the insulin measurement method, cannot be used in individuals with extensive damage to beta cells and is more suitable for a large group epidemiologic research on IR, which is a limitation of this study.

A study conducted on large number of subjects with NGT, IGT and DM that investigated direct insulin sensitivity and its correlation with fasting insulin levels and insulin levels post glucose load, well known risk factors for CHD, has found that there is a very significant independent association between insulin sensitivity and CHD and between CHD and fasting insulin and has confirmed that hypertension, dyslipidaemia and hypergly-

caemia play a role in these relationships, unlike some studies that have denied indirect relationship between these dysmetabolic states.[39, 40] This study has also shown that IGT together with IR and other metabolic disorders could contribute to the development of CHD to a certain extent.

De Fonzo[41] suggests that high CHD risk in diabetics is caused by IR rather than by hyperglycaemia and that CHD rates double if obesity, dyslipidaemia and hypertension are also present in those patients. He believes that elevated insulin levels lead to an alternative pathway of insulin signalling, activating mitogen activated protein kinase (MAPK), whose activity is central to mitogen-proatherosclerotic pathway.

Diabetes impairs utilisation of lipids and lipoproteins causing diabetes induced atherogenic dyslipidaemia, which is one of the most important risk factors for atherosclerosis in people with DM.[42, 43] Atherosclerosis is one of the main causes of the development of CVD.[44] Diabetic dyslipidaemia is characterised by increased levels of serum low-density lipoproteins (LDL) and triglycerides (TG) and decreased levels of high-density lipoproteins (HDL).[45]

Also, recently conducted prospective studies have shown that patients with DMT2 who developed CHD had higher levels of very low-density cholesterol (VLDL-h) with lower levels of high-density lipoprotein cholesterol 2 (HDL2) compared to individuals who did not develop CHD.[46] This association is noted in both type 2 diabetics and nondiabetics. The most significant predictive risk factor for CHD is increased levels of total and VLDL TG which manifest their atherogenic effect by inducing a decrease in HDL cholesterol and an increase in small, dense LDL particles, as well as an increase in production of apolipoprotein B. Research has shown that combined changes in lipid profile, ie small, dense LDL-h particles and prediabetes have a strong effect on the development of CHD.[47]

This study has found that total cholesterol levels were the highest in subjects with IGT, whereas total triglyceride levels were the highest in subjects with CHD. HDL cholesterol levels were the lowest in subjects with IGT and CHD, in accordance with previously mentioned studies.

The role of immune system is so important that atherosclerosis is nowadays considered primarily an inflammatory phenomenon.[48] Inflammatory model is useful in interpreting a large number of epidemiological data and it explains why serum levels of proteins, such as ceruloplasmin, fibrinogen and albumin are associated with cardiovascular risk.[49] Meta analysis of 14 prospective long-term studies has found that, after adjusting for age, smoking, cardiovascular risk factor CRP is strongly associated with CHD.[50, 51] Apart from pro-atherosclerotic effect of CRP, primarily in the early stages of atherogenesis, researchers have recently discovered that CRP could also play a role in the later stages of atherosclerosis. In 2003 the American Heart Association (AHA) and the Centre for Disease Control (CDC) recommended that inflammation markers be used together with other markers for cardiovascular risk assessment.[52] In accordance with that, the present study has shown that chronic inflammation factors are higher in IGT with CHD group and together with IR, they could be potential risk factors for the development of CHD in IGT. The study conducted in 2016 has found no association between serum fibrinogen and glucose impairment.[53]

Elevated hsCRP levels were associated with prediabetes in correlation with age, obesity and abnormal lipid profile, which was proven in Aishwarya Ghule study in 2021[54] and is comparable to this study where the levels were the highest in IGT with CHD group where atherosclerosis had, probably, already started developing.

Up until a few years ago, it was believed that the CHD typically affected men and most medical papers had adopted the idea that women could suffer more from breast cancer than from CVD. In 2004 the World Health Organization reported total CVD mortality in Europe: 55 % in women and 43 % in men. CHD, stroke and other CVD represent 23 %, 18 % and 15 % of cases in women and 21 %, 11 % and 11 % of cases in men.[55] After ages 45 for men and 55 for women CHD risk increases in similar fashion in both groups. It is presumed that oestrogen has cardioprotective effect in premenopausal women (usually under the age of 55). It is of utmost concern that CHD mortality rates in young women aged 35 to 45 continue to rise.[56-58] Older age, hypertension, total and LDL cholesterol have the biggest effect on men, whereas menopause, systolic hypertension, smoking, diabetes, triglycerides and HDL cholesterol levels mostly have an effect on women. Failure to recognise early symptoms and to adequately assess CHD in young women, despite well

known risk factors, could contribute to this disturbing trend.[57] By middle age more than 80 % of women have 1 or more traditional risk factors for heart attack.[59] Diabetic women are more than six times more likely to die from CHD compared to women without diabetes.[60] There is evidence that the loss of oestrogen at any age contributes to endothelial dysfunction. In the Women's Health Study, a global risk prediction model, which has included hsCRP, improved prediction of cardiovascular risk in women.[61] Also, hsCRP was found to be a stronger cardiovascular event predictor in women than LDL cholesterol. After menopause, the lack of oestrogen leads to structural and functional changes in the cardiovascular system: endothelial dysfunction, imbalance of autonomic activity towards increased adrenergic activity, visceral obesity, increased systemic inflammation. All these factors contribute to the development of systemic hypertension, IGT, abnormal lipid profile and IR.

CHD group included mostly smokers and the difference between sexes was minimal in favour of men, in accordance with most previous studies. In individuals aged 45 to 54, 38.2 % of cardiovascular mortality in men and 33.7 % in women could be attributed to smoking.[62] Although the greatest risk burden is seen in middle age, smoking is a strong independent risk factor for cardiovascular events and mortality even in older age, increasing cardiovascular mortality for more than five years in smokers older than 60.[63] In all age groups, women smokers are at significantly higher risk of CHD events (fatal and nonfatal), compared to non-smoking women.[64] Smoking is more harmful to women than to men, with relative risk of cardiovascular events of 3.6 in women and 2.4 in men. While cardiovascular risk remains similar in men regardless of daily cigarette consumption, that risk increases in women with the number of cigarettes smoked per day ranging from relative risk of 2.3 for 1-9 cigarettes per day to 5.9 for more than 20 cigarettes per day.[65]

Several limitations of this report that cannot be considered definitive are to be acknowledged. Firstly, limited size of statistically representative sample.
In fact, data gathered here will be used as the basis for larger, more definitive study that will include remaining risk factors such as stress, concentrations of counterregulatory hormones that affect glucoregulation, menopause and the like.

Secondly, the limitation lies in inhomogeneous patient distribution among groups. The goal was to recruit representative sample of patients with IGT and CHD. Thus, the control group included significantly more women, fewer smokers and younger subjects compared to the other groups. Without a clear insight into the lifestyle, daily stress and regularity of menstrual cycles, considering that perimenopausal women were included in the study, the effect of oestrogen cardioprotection could not be asserted with certainty. The remaining three groups were homogenous regarding investigated parameters, sex, age and smoking habits. Limited sex specific data on the CHD risk associated with IGT, that were analysed in this study, did not support any significant difference between sexes. As a guideline, the results of the 2001 DECODE study were used that had determined that relative risks of CHD among participants with 2-hour glucose abnormalities corresponding to IGT, were very similar in men and women.[66] More studies are needed to better elucidate sex specific risks that can be attributed to IFG and IGT. This study did not address the question whether the risk of developing CHD was limited to individuals with IGT who developed diabetes or if it was still increased in individuals with IGT even if they never developed diabetes. Potential confounding factor such as physical activity, stress that could have significant effect on the sensitivity of peripheral tissues to insulin, is one of the limitations of this study. An economic analysis that would include diabetes prevention and CVD could provide additional useful information that would help guide future discussions of the need for screening for IGT in general population or in specific high-risk population groups.

Conclusion

Metabolic disorders, together with inflammation mediators, are possible predictors of the development of IGT. Decreased sensitivity of peripheral tissues to insulin and the resulting hyperinsulinism, increased concentrations of triglycerides and LDL cholesterol and decreased HDL cholesterol, as well as an increase in hsCRP and fibrinogen concentrations in patients, have all potentiated development of glucose tolerance disorders and potential

effect on accelerated development of atherosclerosis in the vascular system of the heart of those patients. In practice, this requires the earliest possible detection of patients with hyperinsulinaemia and normal glucose tolerance in order to start a timely intervention to reduce glucotoxicity, lipotoxicity and IR, thus preventing the development of DMT2 and associated complications.

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None.

Conflict of interest

None.

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