# Glucose Metabolism in Patients with Acute Coronary Syndrome Without Having History of Diabetes mellitus

## Diabetes mellitus Hikayesi Olmayan Akut Koroner Sendromlu Hastalarda Glukoz Metabolizması

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Geliş Tarihi/*Received:* 09.02.2011
Kabul Tarihi/*Accepted:* 10.07.2011

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**ABSTRACT Objective:** Studies have shown that increased fasting blood glucose levels, even in the normal range and impaired glucose tolerance have increased risk of cardiovascular disease and mortality. In this study we planned to characterize the glucometabolic profile of patients with acute coronary syndrome without any history of diabetes mellitus and to assess whether an oral glucose tolerance test would improve the detection of abnormal glucose regulation in patients without known diabetes. **Material and Methods:** We enrolled 140 patients with acute coronary syndrome and a standardized oral glucose tolerance test was performed between 12-14 days. Four teen of the patients admitted to our coronary unit had unstable angina pectoris (10%), 30 of them had non-ST elevated myocardial infarction (21.4%), 96 of them had ST elevated myocardial infarction (68.6%). **Results:** In patients with acute coronary syndrome we found that 48 patients had normal glucose tolerance (34.3%), 27 had impaired fasting glucose (19.3%), 43 had impaired glucose tolerance (30.7%) and 22 had diabetes mellitus (15.7%). Homeostasis model assessment levels of the patients with normal glucose tolerance, impaired fasting glucose/impaired glucose tolerance and diabetes mellitus were as follows; 1.93 ± 0.8, 3.4 ± 0.1, 3.8 ± 0.9 respectively. In all types of acute coronary syndromes and types of glucose metabolism the majority of the patients had had one disease involvement. **Conclusion:** We found that in patients who did not have any history of diabetes, unknown impaired glucose regulation resulting with endothelial dysfunction and atherosclerosis might force the patients admit to an hospital with acute coronary syndrome so it may be wise to perform oral glucose tolerance test before leaving the hospital in patients with acute coronary syndrome. This strategy may offer us the chance of improving the prognosis of patients with acute coronary syndrome.

**Key Words:** Diabetes mellitus; acute coronary syndrome; glucose metabolism disorders

**ÖZET Amaç:** Çalışmalar göstermiştir ki, normal sınırlarda bile olsa artmış açlık glukoz seviyesi ve bozulmuş glukoz toleransı yüksek kardiyovasküler hastalık ve ölüm riski oluştururlar. Çalışmamızda diabetes mellitus hikayesi olmayan akut koroner sendromlu hastalarda glukometabolik profili karakterize etmeyi ve bu hastalarda oral glukoz tolerans testinin anormal glukoz regülasyonunun tesbitinde etkin olup olamayacağını tayin etmeyi planladık. **Gereç ve Yöntemler:** Çalışmamıza akut koroner sendromlu 140 hasta alındı ve 12-14. günler arasında standardize oral glukoz tolerans testi yapıldı. Koroner bakım ünitesine alınan hastaların 14'ünde kararsız anjina pektoris (%10), 30'unda ST elevasyonu olmayan miyokard infarktüsü, (%21,4), 96'sında ST elevasyonlu miyokard infarktüsü (%68,6) vardı. **Bulgular:** Akut koroner sendromlu hastalarımızın 48'inde (%34,3) normal glukoz toleransı, 27'sinde bozulmuş açlık glukozu (%19,3), 43'ünde bozulmuş glukoz toleransı (%30,7) ve 22'sinde (%15,7) diabetes mellitus saptandı. Normal glukoz toleransı, bozulmuş açlık glukozu/bozulmuş glukoz toleransına sahip hastaların insülin rezistansı indeksleri sırasıyla 1,93 ± 0,8, 3,4 ± 0,1 ve 3,8 ± 0,9 olarak belirlenmiştir. Gerek farklı akut koroner sendrom tipleri ve gerekse farklı glukoz metabolizma tiplerine sahip hastalarda en sık olarak tek damar tutulumuna rastlanılmıştır. **Sonuç:** Bilinen diyabeti olmayan hastalarımızda, bilinmeyen bozulmuş glukoz regülasyonunun neden olduğu endotel disfonksiyonu ve aterosklerozun bu hastaların karşımıza akut koroner sendromla çıkmalarına neden olabileceğini düşündük, bu nedenle akut koroner sendromlu hastalarda hastaneyi terk etmeden önce oral glukoz tolerans testi yapılmasının akıllıca olacağı fikrindeyiz. Bu strateji, bize akut koroner sendromlu hastalarda prognozu iyileştirme şansını sunabilir diye düşünüyoruz.

**Anahtar Kelimeler:** Diabetes mellitus; akut koroner sendrom; glukoz metabolizması bozuklukları



**Turkiye Klinikleri J Cardiovasc Sci 2011;23(3):170-6**

Diabetic patients have a higher incidence of acute coronary syndrome (ACS) than non-diabetic patients.[1-3] Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are considered to be pre-diabetic states. Studies have shown that relatively elevated fasting blood glucose (FBG) levels, even in the normal range and IGT have increased risk of cardiovascular disease and mortality.[1,4-6] Early identification of these metabolic abnormalities would enable initiation of potentially benefical treatment contributing to an improved prognosis.

There is a positive relation between admission blood glucose at hospital for ACSs and long-term mortality in patients with and without diabetes.[7,8] Both FBG, random blood glucose and oral glucose tolerance test (OGTT) have been utilised for assessment of glucose regulation in patients presenting with ACS. Random blood glucose seems to be non-spesific and non-sensitive. Studies have found that if FBG alone is used, up to 84 % of patients with abnormal glucose regulation may remain undetected.[1,2,4,8]

There have been no systematic studies about the prevelance of impaired glucose regulation (IGR) in an ACS population in Turkey. The aims of this study were first, to characterize the glucometebolic profile of patients with ACS without any history of diabetes second, assess whether an OGTT would improve the detection of abnormal glucose regulation in patients without known diabetes.

## MATERIAL AND METHODS

### PATIENTS

We enrolled 140 patients admitted to the coronary unit of Ankara Training and Research Hospital for suspected ACS between June 2009 and September 2009. 115 of them (82.1%) were male and 25 of them (17.9%) were female. 14 of the patients admitted to our coronary unit had unstable angina pectoris (USAP) (10%), 30 of them had non-ST elevated myocardial infarction (NSTEMI) (21.4%), 96 of them had ST elevated myocardial infarction (STEMI) (68.6%).

We excluded patients with previously known diabetes or glucose intolerance, conditions which may affect metabolic parameters (such as thyroid dysfunctions in history or nowadays), pregnancy, infection, having conditions preventing an OGTT and taking medications that may interfere metabolic parameters. We did not recruit patients who had chronic renal failure or who were older than age of 80. All the subjects gave written informed consent and this study was performed according to the principles of Declaration of Helsinki 2008. Ethical approval for the study was obtained from Ankara Training and Research Hospital Ethics Committee.

The first day after admission, fasting venous blood samples were collected for fasting blood glucose (FBG), HbA1c and fasting insulin (FI). A standardized 75 g OGTT was performed between 12-14 day to minimize any possible confounding effects of ACS on the glucose metabolism. Body weight, height, waist, hip circumference were measured before discharge. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Waist and hip circumference were measured when fasting by a non-elastic measurement, as upright position.

The diagnosis of ACS was based on the joint recommendations by the European Society of Cardiology and American College of Cardiology.[9] On admission ACS diagnosis was classified into STEMI, NSTEMI and USAP. STEMI was defined as chest pain (or angina-equivalent symptoms) with ST elevation >1 mm in >2 contiguous leads or new left bundle branch block (LBBB) and an elevated troponin T (>0.03 mg/L). NSTEMI was defined as chest pain with an elevated troponin without ST elevation >1 mm in >2 leads or new LBBB. USAP was defined as chest pain, without a troponin rise and with electrocardiographic changes of acute ischaemia (ST elevation or depression, T wave inversion), or history of coronary artery disease, or age >65 years, or at least 2 vascular risk factors (hypertension, hyperlipidaemia, family history, smoking, diabetes).

All glucometabolic classifications according to American Diabetes Association (ADA)[10,11] criteria were based on the measurement of blood glucose

before or 2 h after glucose intake to be reported as normal glucose regulation, normal fasting glucose, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or diabetes mellitus. Individuals with fasting blood glucose concentrations of < 5.6 mmol/l (< 100 mg/dl) were considered to be normal, concentrations between 5.6-6.9 mmol/l (100-125 mg/dl) were considered to be IFG and concentrations of ≥7.0 mmol/l (≥126 mg/dl) were considered to be diabetes. 2 hour postload glucose values of the OGTT according to the World Health Organization (WHO)[12] and ADA[10,11] definitions were as follows; normal glucose tolerance < 7.8 mmol/l (140 mg/dl), impaired glucose tolerance 7.8-11.0 mmol/l (140-200 mg/dl), and diabetes > 11.1 mmol/l (200 mg/dl). Plasma insulin was analyzed in fasting samples taken on the first morning after admission.

Insulin resistance expressed as the homeostasis model assessment for insulin resistance (HOMA-IR) was calculated under fasting conditions as plasma insulin (microunits per milliliter) x blood glucose (millimoles per liter) / 22.5.[13]

### CORONARY ANGIOGRAPHY

An analysis of the coronary angiograms was performed by an independent experienced observer. The presence of coronary artery disease was defined as > 75% diameter narrowing. The coronary arteries were grouped as the left anterior descending or diagonal and septal branches, the left circumflex artery or obtuse marginal branch, and the right coronary artery or posterior descending and posterolateral branch to define one, two, and three vessel disease, respectively.[14]

### STATISTICAL ANALYSIS

Data were presented as number of patients and percentages.

## RESULTS

This study was performed with 140 patients with ACS, 44 of them having USAP + NSTEMI (31.4%) (as their clinical courses were similar we decided to handle them together), 96 of them having STEMI (68.6%). Out of 140 patients 115 was male (82.9%) and 25 was female (17.9%). In both males and females the rate of STEMI were high. USAP+ NSTEMI were diagnosed in 36 males (81.8%) and 8 females (18.2%). STEMI was diagnosed in 79 males (82.3%) and 17 females (17.7%). Forty of the patients were treated by medical treatment (28.3%), 74 of them had percutaneous coronary intervention (52.9%) and 26 of them had coronary artery by-pass grafting (18.6%).

Coronary angiography of the patients revealed the number of the stenosed coronary vessels diseased. 92 of the patients had one vessel (65.7%), 32 of them had two vessel (22.9%) and 16 of them had 3 vessel disease (11.4%). In USAP+ NSTEMI patients, 26 had 1 vessel (59.1%), 10 had 2 vessel (22.7%), 8 had 3 vessel (8.2%) disease. In STEMI patients 66 of them had 1 vessel (68.8%), 22 had 2 vessel (22.9%), 8 had 3 vessel (8.3%) disease.

After OGTT performed just after the patients were discharged (between 12-14 day) we found that 48 patients had normal glucose tolerance (34.3%), 27 had IFG (19.3%), 43 had IGT (30.7%) and 22 had DM (15.7%).

In Table 1, characteristics of all the patients were represented. Among all patients with the mean age of 54.5 ± 7.6 years and the oldest group with mean age of 62.0 ± 11.0 was DM. The majority of the patients had FBG/IGT both in female or male sex. HOMA levels of the patients with normal glucose tolerance, impaired fasting glucose/ impaired glucose tolerance and diabetes mellitus were as follows; 1.93 ± 0.8, 3.4 ± 0.1, 3.8 ± 0.9 respectively. The total BMI was 28.7 ± 4.5kg /$m^2$, but diabetic patients were the most obese ones (30.3 ± 1.2 5 kg /$m^2$). Furthermore the diabetic patients had the highest waist, hip circumference and HOMA-IR (98.9 ± 3.4 cm, 104.1 ± 0.9 cm and 3.8 ± 0.9 respectively) (Table 1).

In Table 2 results of OGTT according to ACS types were presented. Out of 44 patients having USAP + NSTEMI, 12 of them were diagnosed as having normal glucose metabolism (27.3%), 7 of them having IFG (15.9%), 15 of them having IGT (34.1%) and 10 of them having DM (22.7%). Out of 96 patients having STEMI, 36 of them were di-

**TABLE 1:** Clinical characteristics and metabolic data at admission.

| | Normal | IFG/IGT | DM | Total |
|---|---|---|---|---|
| Patients | 48 | 70 | 22 | 140 |
| Age (year) | 49.6 ± 8.5 | 55.6 ± 10.1 | 62.0 ± 11.0 | 54.5 ± 7.6 |
| Male | 45 | 54 | 16 | 115 |
| Female | 3 | 16 | 6 | 25 |
| STEMI | 36 | 48 | 12 | 96 |
| USAP+ NSTEMI | 12 | 22 | 10 | 44 |
| BMI | 28.2 ± 2.3 | 28.6 ± 2.4 | 30.3 ± 1.2 | 28.7 ± 4.5 |
| Waist circumference (cm) | 92.1 ± 6.4 | 94.9 ± 7.9 | 98.9 ± 3.4 | 94.5 ± 8.7 |
| Hip circumference (cm) | 99.6 ± 1.1 | 99.5 ± 1.2 | 104.1 ± 0.9 | 101.3 ± 1.0 |
| HbA1c (%) | 5.4 ± 0.2 | 5.6 ± 0.3 | 6.2 ± 0.4 | 5.6 ± 1.5 |
| Fasting insulin (pmol/l) | 8.5 ± 3.9 | 12.8 ± 4.6 | 15.8 ± 3.6 | 12.8 ± 4.3 |
| HOMA-IR | 1.93 ± 0.8 | 3.4 ± 0.1 | 3.8 ± 0.9 | 3.1 ± 0.4 |
| FBG (mg/ dl) | 90.9 ± 2.5 | 99.2 ± 10.1 | 107.0 ± 11.9 | 98.2 ± 9.1 |
| Number of stenosed vessels | 1.5 ± 0.7 | 1.3 ± 0.6 | 1.5 ± 0.7 | 1.5 ± 0.6 |

IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, DM: Diabetes mellitus, STEMI: ST elevated myocardial infarction, NSTEMI: Non- ST elevated myocardial infarction, USAP: Unstable angina pectoris, BMI: Body mass index, HOMA-IR: Homeostasis model assessment insulin resistance index, FBG: Fasting plasma glucose.

agnosed as having normal glucose metabolism (37.5%), 20 of them having IGT (20.8), 28 of them having IGT (29.2) and 12 of them having DM (12.5%) (Table 2).

In Table 3, results of OGTT according to vessel involvement were presented. The majority of the patients who were classiffied as having normal glucose regulation, or IFG, or IGT or DM had one vessel disease. Approximately one third of the patients who had 1 vessel disease were diagnosed as normal glucose regulation, one third as IGT. The majority of the patients with 2 and 3 vessel had normal glucose regulation (Table 3).

## DISCUSSION

Diabetic patients have a higher incidence of ACS than non diabetic patients and individuals with diabetes who have myocardial infarction are more likely to die than those without diabetes.[1-3,15] Furthermore, people with prediabetic conditions such as IFG and IGT have a raised risk of cardiovascular disease.[1,4,6,16-19] There is also a relation between plasma glucose concentrations at the time of admission to hospital for acute MI and risk of death in patients with and without diagnosed diabetes.[19-21] In DIGAMI study, glucometabolic state at admission was suggested to be a long-term risk marker and when the patients with diabetes and acute MI were randomised to insulin treatment, an important mortality reduction was obtained.[21]

In our study we intended to characterize the glucometabolic profile of patients with ACS, without any history of diabetes. We demonstrated that in our patients with ACS, prevalence of IFG, IGT, DM and IFG+IGT were as follows; 19.3%, 30.7%

**TABLE 2:** Results of of OGTT according to ACS types.

| | Normal | IFG | IGT | DM | Total |
|---|---|---|---|---|---|
| USAP+NSTEMI | 12 (27.3%) | 7 (15.9%) | 15 (34.1%) | 10 (22.7%) | 44 |
| STEMI | 36 (37.5%) | 20 (20.8%) | 28 (29.2%) | 12 (12.5%) | 96 |
| Total | 48 | 27 | 43 | 22 | 140 |

USAP: Unstable angina pectoris, NSTEMI: Non ST elevated myocardial infarctus, STEMI: ST elevated myocardial infarctus, IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, DM: diabetes mellitus.

**TABLE 3:** Results of of OGTT according to ACS types.

| | Normal | IFG | IGT | DM | Total |
|---|---|---|---|---|---|
| 1 vessel | 32 (34.8%) | 18 (19.6%) | 32 (34.8%) | 10 (10.8%) | 92 (100%) |
| 2 vessel | 12 (37.5%) | 7 (21.9%) | 5 (15.6%) | 8 (25.0%) | 32 (100%) |
| 3 vessel | 6 (37.5%) | 2 (12.5%) | 4 (25.0%) | 4 (25.0%) | 16 (100%) |
| Total | 48 | 27 | 43 | 22 | 140 |

IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, DM: diabetes mellitus.

and 15.7% respectively. 34.3% of our patients with ACS had normal glucose tolerance. In three large studies named The Euro Heart Survey,[4] GAMI study,[8] The China Heart Survey[2] rates of diabetes were 22%, 31% and 28% respectively. Comparing the decreased rate of DM in our study with these large studies, we point out that our patients are younger, with mean age of 54.5 years. The mean age of The Euro Heart Survey, GAMI study, The China Heart Survey were; 66, 63.5 and 69 years respectively. In the literature rates of diabetes were demonstrated as 5-37%.[1,7,8,20,22,23] The high ratio range of DM may be explained with the different time of the OGTTs performed, age, gender, race, BMI and concomittant diseases of the patients. This may also partially be explained by the use of different glucose threshold levels for diagnosis of diabetes. In our study mean age was 54.5 years, mean BMI was 24.0 kg/m$^2$ and female/male ratio was 17.9/82.1%. In previous studies mean age was 46.0-67.3 years, BMI was 23.5-27.4 kg/m$^2$ and female/male ratio was 29-33.4/68-71% respectively.[1,3,4,7,8,24-26]

In Funagata study, it was demonstrated that IGT but not IFG was a risk factor for death from cardiovascular disease.[25] 19.3 % of our patients had IFG and 30.7 % had IGT. Considering the majority of our patients we may speculate that patients in whom IGT was diagnosed when they were admitted to the hospital with ACS must be handled with more care.

Uncertainty still remains over the ideal test in order to diagnose real glucose metabolism in patients with ACS. FBG, random blood glucose and OGTT were recomended. Random blood glucose lacks sensitivity and spesifity. The diagnostic criteria of IFG has been a subject of debate.[10,11,12,27,28] WHO recommended a higher diagnostic treshold of IFG than ADA.[10-12] In Joint British Societies guide it was stated that FBG may be a useful alternative to OGTT in patients with ACS,[29] but studies have found that if FBG alone is used, up to 84% of patients with abnormal glucose tolerance may remain undiagnosed.[1,2,4,8] Although OGTT may be more predictive than other tests, it is inconvenient for the patient and it has problems about reproducibility. In spite of these findings, OGTT may be advocated because FBG may underestimate abnormal glucose regulation. Chih et al. found discordance in abnormal glucose regulation detected with admission FBG and subsequent OGTT and showed that FBG on admission had had only a modest sensitivity and spesificity for the detection of IGT/DM on subsequent OGTT.[1] Furthermore in this study DM was detected in 25% of patients who had normal FBG on admission. In another study, 10% DM was detected with FBG in patients with ACS, but after OGTT this rate increased to 33%.[30] We think that although FBG has good reproducibility, small variability and easy application, fasting state is difficult to assure in a population study, and it will not be more reliable than OGTT, so we insisted in OGTT in order to fully detect and characterize abnormal glucose tolerance in ACS patients. In our study if we were satisfied with FBG, 27 patients with IGT would have been undiagnosed. In DECODE study, a high 2 hour glucose concentration was found to be associated with an increased risk of death, independent of the level of fasting blood glucose, whereas mortality associated with the fasting glucose concentration depend on the level of 2 hour, in all categories of fasting glucose. [31] This study presents us another reason for evaluating the patients with OGTT.

The optimal time for exact assessment of glucose regulation in patients with ACS is unclear. Acute hyperglyceamia post MI is common and regarded as a response to adrenergic stress. Acute stress also effects OGTT. In the literature OGTT was performed in 4 days-4 weeks after admission.[1,4,8,20,22,32] In order to eliminate the interference of the effects of acute stress, left ventricular disfunction and inflammation we chose to perform OGTT approximately 2 weeks after the ACS, not too late or too early.

In European Heart Survey, OGTT was performed in 4-5 days, and its results were found to be correlated with 3-12 months glyceamic condition of ACS patients,[4] but there are studies disagreeing it. In GAMI trial, the number of diabetic patients with ACS lessened up to 25% from 31% in 3 months.[5,6] Chih et al. demonstrated that 50% of the patients with IFG in admission showed normal glu-

cose regulation after 4 weeks.[1] There are more studies demonstrating lessened abnormal glucose rates 3 months after ACS.[23,33,34] In our study 2 weeks after admission 15.7% DM was diagnosed. According to these results we recommend to perform OGTT in two weeks.

Mortality risk of coronary artery disease depends on left ventricular function, anatomical variations of coronary arteries, amount of muscle effected by the infarct, collateral vessel conditions, besides involved coronary arteries. So mortality risk of a patients with one vessel involvement may be higher than a patient with 3 vessel involvement. In our study we found that the patients with 1, 2 and 3 vessel disease DM was not in majority. Zaliunas et al. demonstrated similar results in diabetic ACS patients; 48.9% of the patients had one vessel, 22.2% had 2 vessel and 22.9% had 3 vessel disease. [35] In the literature there are studies demonstrating higher rates of multiple vessel involvements in patients with DM and ACS.[36-40] The discrepancy of the rate of vessel involvements in patients with DM and ACS may be due to age, sex, BMI, smoking, and related diseases of the patients. Otherwise, in our diabetic patients HbA1c was 6.2% ± 0.47, and FBG was 107.0 ± 11.9. Their blood sugar regulation were not bad, and as diabetes mellitus was not diagnosed prior their admission at the hospital, their disease must have not lasted too long. These results may explain why our diabetics had less number of involved vessels.

In conclusion, in order to determine glucose metabolism status of the patients with ACS, we recommend to perform OGTT before the patients are discharged. This will provide us the chance of early diagnosing patients with abnormalities of glucose metabolism, protecting them from harmful effects of insulin resistance, successful handling of cardiometabolic risks. Our results demonstrated that, glucose metabolism abnormalities were found in high rates in our population with ACS and that random glucose concentration at admission and fasting blood glucose do not determine the prevalence of diabetes but, may be useful in choosing patients who needs OGTT.

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