ARAŞTIRMA / RESEARCH

# Relationship between nicotine dependence and complexity of coronary artery disease

Nikotin bağımlılığının koroner arter hastalığı ciddiyetiyle ilişkisi

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**Abstract**

**Purpose:** Smoking cessation is essential to prevent coronary artery disease and its poor outcomes however, it is difficult to quit for some smokers due to higher degree of nicotine dependence. Although smoking has been well demonstrated to be associated with coronary artery disease, its association with nicotine dependence is unknown. Recent studies show that the Syntax score is a new tool for the risk stratification of patients with complex coronary artery disease. In this retrospective study, we aimed to evaluate whether Fagerström test score for nicotine dependence was associated with the complexity of coronary artery disease as evaluated by Syntax score.

**Material and Methods:** The study population consisted of smoking status patients with currently smoking who underwent coronary angiography. Patients were divided into four groups according to Syntax score tertiles: as control group (Syntax score 0; n = 25) low risk group 1(Syntax score 1-22; n = 25), intermediate risk group 2 (Syntax score 23-32; n = 25) and high risk group 3 (Syntax score > 32; n = 25). Fagerström test was conducted for nicotine dependence at outpatient visits and phone callings by one physician.

**Results:** The Fagerström test score was prominently related with Syntax score and was a significant predictor of Syntax score after adjustment for other risk factors.

**Conclusion:** The Fagerström test score was significantly associated with the complexity of with coronary artery disease evaluated by Syntax score. Further prospective studies are needed to verify this finding.

**Key words:** Fagerström score, coronary angiography, Syntax score, nicotine dependence

**Öz**

**Amaç:** Sigaranın bırakılması, koroner arter hastalığını ve kötü sonuçlarını önlemek için oldukça önemlidir, ancak yüksek nikotin bağımlılığı nedeniyle sigara içen bazı hastalar için sigarayı bırakmak zor olmaktadır. Sigaranın koroner arter hastalığı ile ilişkili olduğu iyi gösterilmiş olsa da, nikotin bağımlılığı ile olan ilişkisi bilinmemektedir. Son çalışmalar, Syntaks skorunun kompleks koroner arter hastalığı olan hastaların risk katmanlandırılması için yeni bir araç olduğunu gösteriyor. Bu retrospektif çalışmada Fagerström test skorunun, Syntaks skoru ile değerlendirilen koroner arter hastalığı ciddiyeti ile ilişkili olup olmadığını değerlendirmeyi amaçladık.

**Gereç ve Yöntem:** Çalışma popülasyonu, halen sigara içmekte olan ve koroner anjiyografi yapılan hastalardan oluşmaktadır. Hastalar Syntaks skorlarına göre dört gruba ayrıldı: kontrol grubu (Syntaks skoru = 0, n = 25) düşük riskli, grup 1 (Syntaks skoru 1-22, n = 25), orta riskli, grup 2 (Syntaks skoru 23-32 N = 25) ve yüksek riskli, grup 3 (Syntaks skoru > 32; n = 25). Fagerström testi, çalışmaya katılan bir hekim tarafından poliklinik kontrollerinde ve telefon görüşmelerinde yapıldı.

**Bulgular:** Fagerström test puanı Syntaks skoruyla belirgin bir şekilde ilişkiliydi ve diğer risk faktörleri için düzeltme yapıldıktan sonra Syntaks skorunun önemli bir öngördürücüsü olarak tespit edildi.

**Sonuç:** Fagerström test puanı, Syntaks skoruyla değerlendirilen koroner arter hastalığının ciddiyeti ile anlamlı derecede ilişkili bulunmuştur. Bu bulguyu doğrulamak için daha ileri prospektif çalışmalara ihtiyaç vardır.

**Anahtar kelimeler**: Fagerström skoru, koroner anjiyografi, Syntaks skoru, nikotin bağımlılığı

## INTRODUCTION

Smoking is implicated morbidity and mortality in the general population as well as in patients with coronary artery disease (CAD)[1]. Many studies demonstrated that smoking population contain groups of smokers for whom it is harder to quit, potentially because they have a higher degree of nicotine dependence. The Fagerström test for nicotine dependence is a standard instrument for assessing the intensity of physical addiction to nicotine related to cigarette smoking, quantity of cigarette consumption, the compulsion to use, and dependence[2-8].

The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) score is an angiographic grading system based on the severity and complexity of the characteristics of coronary artery lesions[9,10] including the number of lesions, total occlusion, bifurcation, trifurcation, aorta-osteal stenosis, tortuosity, calcification, thrombus, diffuse lesion, and small vessel/diffuse disease. The score system is derived entirely from the coronary anatomy and lesion characteristics[11-15]. This system is widely accepted as a CAD complexity marker, and its prognostic value has been demonstrated in different clinical situations, and patients with the higher Syntax score have significantly more major adverse cardiac events (MACE)[16,17].

However it is well known that cigarette smoking is strongly associated with the development of cardiovascular disease, there is no adequate data demonstrating the relationship between nicotine dependence and coronary artery diseases. In this study, we goaled to evaluate whether nicotine dependence was associated with the complexity of CAD as evaluated by the Fagerström test and Syntax score.

## MATERIAL AND METHODS

### Subjects

We retrospectively reviewed the data of smoking patients who underwent coronary angiography at our institute between January 2016 and March 2016. Patients were adjusted into four groups according to Syntax score tertiles: SS control (SS 0; n = 25), SS group 1(SS 1-22; n = 25), SSgroup2 (SS 23-32; n = 25) and SS group3 (SS > 32; n = 25).

The indications for angiography in individuals in clinically stable condition were chest pain and/or noninvasive test results consistent with myocardial ischemia. Exclusion criteria was any previous history of coronary revascularization and being in the first four weeks of acute coronary syndrome.

### Baseline definitions and cardiovascular risk assessments

Hypertension was defined as systolic pressure ≥ 140 mm Hg and / or diastolic pressure ≥ 90 mm Hg or if the individual was taking antihypertensive medications. Those with a fasting LDL level > 130 mg / dL or history of statin use were considered to be hypercholesterolemic. Diabetes mellitus (DM) was defined as fasting plasma glucose ≥ 126 mg / dL and those who were on treatment for established DM were considered to be diabetics. Subjects were accepted as smokers if they had smoked at least one cigarette per day in the year performed coronary angiography. Body mass index was calculated as weight (kilograms) divided by height (meters squared). Demographic data, including age, gender, comorbidities, weight, and height, fasting serum uric acid, serum creatinine, triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein were collected from the individual charts in the electronic hospital database. Fagerström test was conducted at outpatient visits and phone callings by one physician. The study was approved by our local ethics committee, and oral informed consent was obtained from all patients.

### Syntax score and angiographic analysis

All the Coronary angiograms which performed between January 2016 and March 2016 were analyzed. All angiographic variables pertinent to SS calculation were separately computed by 2 of 3 experienced cardiologists who were blinded to clinical data. In case of disagreement, the opinion of the third observer was obtained, and the final decision was made by consensus. A lesion was defined as significant if it caused a 50 % reduction of the luminal diameter by visual estimation in vessels ≥ 1.5 mm.

Using the Syntax score website (www.Syntaxscore.com) and consistent with the SYNTAX Trial, the low, intermediate and high SS were defined as 1 to 22, 23 to 32 and 33 or more, respectively1. Patients in our work were matched

according to their SS into tertiles defined as control group (SS 0; n = 25), group 1( SS 1-22; n = 25), group 2 ( SS 23-32; n = 25) , and group 3 (SS >32; n = 25).
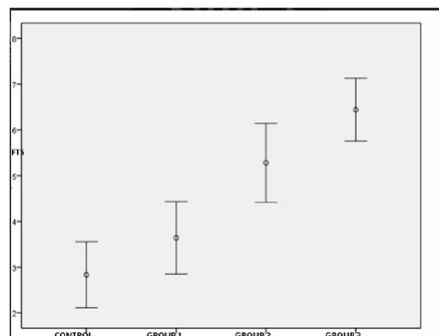


**Figure 1. Fagerström test scores according to the groups.**

## Fagerström test

The Fagerström test for nicotine dependence is a standard instrument for assessing the intensity of physical addiction to nicotine 5-8. It contains six items that evaluate the quantity of cigarette consumption, the compulsion to use, and dependence. This questionnaire has six easily understood questions that can be rapidly applied by physicians can classify nicotine dependence according to a 10-point scale: very low (0 to 2 points), low (3 to 4 points), moderate (5 points), high (6 to 7 points), or very high (8 to 10 points) 4. The higher the total Fagerström score, the more intense is the patient's physical dependence on nicotine.

## Statistical analysis

The data were analysed with IBM SPSS Statistics 21 for Windows. The normal distribution of variables was verified with the Kolmogorov-Smirnov test. Spearman's rho correlation was used when one or both of the variables was / were not normally distributed. We used the Kruskal-Wallis test to account for the differences among the groups, but in order to analysis the specific sample pairs for significant differences we used the Conover-Inman test. $\chi^2$ test was used to investigate whether the distributions of categorical variables differed within the groups.

Moreover logistic regression analysises were conducted according to gender, age, hyperlipidemia, and FTS. Analysis stratified by severity of CAD.

Patients' characteristics are summarized as mean ± standard deviation values or as percentages. P<0.05 was considered to be statistically significant.

## RESULTS

The coronary angiographic records between January 2016 and March 2016, were assessed by three physicians. We designated four groups and those with a syntax score of zero were defined as the control group (SS = 0), group 1 was defined as low SS (1 – 22), group 2 was defined as intermediate SS (23-32), group 3 was defined as high SS (> 33) and 25 patients selected randomly for each groups. Characteristics of subjects, stratified according to SS tertiles, are shown in Table 1. Among the patients who were all smokers, 44.4 % had hypertension, 49.5 % had diabetes mellitus and 69.7 % had hyperlipidemia. Mean age of control group was 57.9 ± 1 1.2, group 1 was 64.0 ± 8, group 2 was 64.84 ± 9.5 and group 3 was 67.32 ± 13.6 (p = 0.016) years.

There were no statistically significant differences between the groups with respect to body mass index, low density lipoprotein, high density lipoprotein, triglycerides, fasting blood glucose, and creatinine levels. We found that the fagerström test score was prominently related with SS (2.83 ± 1.71, 3.64 ± 1.91, 5.28 ± 2.09, 6.44 ± 1.66; P < 0.001) (Table 1) (figure 1). In addition to FTS, male gender [ 9 (36 %), 15 (60 %), 16 (64 %), 18 (72 %), p = 0.039 ), serum uric acid ( 5.10±1.40, 5.59 ± 1.28, 5.94 ± 0.48, P = 0.004) and the prevalence of hyperlipidemia [ 11 (44 %), 18 (72 %), 19 ( 76 %), 21 ( 84 %), 69 ( 69 %); p = 0.027) were significantly related with SS. A significant relationship was observed between the severity of CAD and FTS (p<0.05 was considered to be statistically significant after Conever-Inman test) (Table 2). According to Spearman's rho analysis, a positive correlation between the FTS and the SS was determined to be statistically significant. (r = 0.560, p < 0.001). In the binary logistic regression analysis gender, age, hyperlipidemia, and FTS were the covariates, FTS was found to be an independent predictor of severe CAD (severe CAD were defined as SS ≥ 33) (adjusted odds ratio [OR]: 1.695, 95 confidence interval [CI] 1.314 - 2.187 )

## DISCUSSION

In this study, we assessed whether FTS and other

cardiovascular risk factors were associated with the complexity of CAD as evaluated by SS in a cohort of patients admitted to our department who underwent coronary angiography.

Patients in the SS high tertile (group 3) had higher FTS than patients in the lower two tertiles and the control group. Cigarette smoking is associated with cancer, respiratory diseases, and cardiovascular diseases. Cigarette smoking is considered the leading preventable cause of mortality (Smoking cessation reduces the risk of developing and dying from smoking-related diseases)[19]. Although approximately 70 percent of smokers plan to quit and over 40 percent of smokers report that they tried to quit, the long-term success rate of any unaided quit attempt is low, with only 3 to 7 percent of smokers who make an attempt still abstinent one year later.

**Table 1. Demographics and laboratory characteristics of patients in control, group 1, group 2 and group 3.**

|  | Control (n=25) | Group 1 (N=25) | Group 2 (N=25) | Group3 (N=25) | P value |
|---|---|---|---|---|---|
| Gender (male, n,%) | 9 (36%) | 15 (60%) | 16(64 %) | 18 (72%) | 0.039 |
| Age (years) | 57±11.2 | 64±8.96 | 64±9.56 | 67±13.65 | 0.016 |
| Hypertension (n,%) | 7 (28%) | 11 (44%) | 11 (44 %) | 15 (44 %) | 0.187 |
| Hyperlipidemia (n,%) | 11(44 %) | 18 (72 %) | 19 ( 76 %) | 21 ( 84 %) | 0.027 |
| Diabetes mellitus (n,%) | 13(52%) | 10 (40%) | 12 (48 %) | 14 (56%) | 0.667 |
| Total cholesterol (mg/dL) | 189±44.61 | 195±39.45 | 187±36.86 | 199±53.82 | 0.749 |
| LDL cholesterol (mg/dL) | 108±34.38 | 123±65.57 | 124±33.52 | 115±47.07 | 0.223 |
| HDL cholesterol (mg/dl) | 43±8.92 | 41±8.91 | 39±5.91 | 39±5.08 | 0.245 |
| Triglycerides (mg/dL) | 154±103.67 | 141±73.66 | 143±68.83 | 178±75.28 | 0.195 |
| Fasting blood glucose (mg/dL) | 110±31.61 | 131±71.58 | 126±50.33 | 122±35.03 | 0.418 |
| Serum uric acid(mg/dL) | 5.10±1.40 | 5.59±1.28 | 5.63±0.95 | 5.94±0.48 | 0.004 |
| Serum creatinine (mg/dL) | 0.85±0.20 | 0.93±0.34 | 0.94±0.19 | 0.92±0.12 | 0.285 |
| Fagerström test score | 2.83±1.71 | 3.64±1.91 | 5.28±2.09 | 6.44±1.66 | <0.001 |
| Body mass index (kg/m²) | 26±3.57 | 29±3.27 | 27±5.12 | 26±4.47 | 0.091 |

LDL: Low density lipoprotein, HDL: high density lipoprotein SS: Syntax Score

**Table 2: Post - hoc analysis (pair wise comparison were performed using Conover-Inman test)**

| P values | Control-Group 1 | Control-Group 2 | Control-Group 3 | Group1-Group 2 | Group1-Group 3 | Group 2-Group 3 |
|---|---|---|---|---|---|---|
| Gender (male) | 0.088 | 0.046 | 0.010 | 0.500 | 0.055 | 0.725 |
| Age | 0.025 | 0.026 | 0.864 | 0.986 | 0.015 | 0.016 |
| Hypertension | 0.377 | 0.377 | 0.045 | 0.612 | 0.396 | 0.396 |
| Hyperlipidemia | 0.085 | 0.042 | 0.007 | 0.500 | 0.496 | 0.725 |
| Diabetes Mellitus | 0.396 | 0.778 | 0.563 | 0.776 | 0.396 | 0.778 |
| Total Cholesterol | 0.479 | 0.835 | 0.568 | 0.355 | 0.890 | 0.431 |
| LDL | 0.146 | 0.120 | 0.942 | 0.919 | 0.162 | 0.134 |
| HDL | 0.586 | 0.066 | 0.165 | 0.187 | 0.392 | 0.640 |
| Triglycerides | 0.758 | 0.971 | 0.106 | 0.783 | 0.093 | 0.095 |
| Fasting Glucose | 0.186 | 0.122 | 0.298 | 0.819 | 0.772 | 0.605 |
| Uric acid | 0.075 | 0.394 | <0.001 | 0.342 | 0.057 | 0.005 |
| Creatinine | 0.753 | 0.129 | 0.136 | 0.222 | 0.232 | 0.978 |
| FTS | 0.030 | <0.0001 | <0.0001 | 0.001 | <0.001 | 0.212 |
| BMI | 0.036 | 0.399 | 0.865 | 0.199 | 0.022 | 0.306 |

LDL: Low density lipoprotein, HDL: High density lipoprotein, BMI: Body mass index, FTS:Fagerström test score

With optimal treatment, one-year cessation rates after a single quit attempt can exceed 30 percent[19].

For most of smokers, smoking is both a learned behavior and a physical addiction to nicotine. The Fagerström test for nicotine dependence is a standard instrument for assessing the intensity of physical addiction to nicotine[5-8]. The test was designed to provide an ordinal measure of nicotine dependence related to cigarette smoking. It contains six items that evaluate the quantity of cigarette

consumption, the compulsion to use, and dependence.

The combination of counseling and pharmacologic therapies can produce higher quit rates than either one alone. Pharmacotherapy therapy for smoking cessation, including nicotine replacement therapy, bupropion, and varenicline, aims to reduce the symptoms of nicotine withdrawal, thereby making it easier for a smoker to stop the habitual use of cigarettes[19].

The Syntax score was developed as a comprehensive, angiographic tool grading the complexity of CAD. It aims to assist in patient selection and risk stratification of patients with extensive CAD undergoing revascularization. It is also able to predict MACE after percutaneous revascularization in patients with left main disease and / or multivessel CAD[20].

In our study, high FTS was significantly associated with the complexity of CAD evaluated by SS. SS was the dependent variable was also positively correlated with the level of FTS ( $p < 0.001$, $r = 0.560$). According to the ordinal regression models in our study, FTS was significant predictors of the complexity of CAD as evaluated by SS after adjustment for other risk factors [(adjusted OR: 1.695; 95 % confidence interval [CI] 1.314 – 2.187)].

The smoker's degree of nicotine dependence predicts the difficulty that the smoker will have in quitting and the intensity of treatment likely to be required. Nicotine replacement therapy appears effective in reduction of smoking for those who do not plan to quit. FTS is a valuable test used to disclose whether a smoker trying to quit will need nicotine replacement therapy to treat withdrawal symptoms. In our study, patients with high SS did also have high FTS points. Besides all the other hazards it causes, cardiovascular negative effects of smoking is a well known fact, nicotine replacement therapy should be considered in the treatment of smoker patients with high SS, to quit smoking. The limitations of this study were small number of patients included and its retrospective study

High FTS for nicotine dependence was significantly associated with the complexity of CAD evaluated by Syntax score. Nicotine replacement therapy should be considered in the treatment of smoker patients with high Syntax score, to quit smoking. To support our findigs, further studies with larger patient populations are needed.

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