Prognostic Value of ECGs in Patients With Type-2 Diabetes Mellitus Without Known Cardiovascular Disease

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Introduction and objectives. The predictive value of ECG abnormalities in patients with type-2 diabetes mellitus (DM2) has not been fully studied. Our objective was to assess the prognostic value of ECG abnormalities in patients with DM2 but without known cardiovascular disease.

Methods. Overall, 412 patients with DM2 were identified at 2 primary care centers in the same city. Two hundred and twenty one patients < 80 years of age without known cardiovascular disease were included in the study. An ECG was recorded at baseline and annually during follow-up. The ECGs were evaluated using a system based on the Minnesota code. The main study end-point during follow-up was the occurrence of a cardiovascular event, as defined in the Framingham study.

Results. The mean follow-up duration was 5.9 years (1.1-8.5 years). At the beginning of the study, 24.9% of patients had ECG abnormalities; at the end, 44.3% had abnormalities. Cardiovascular events occurred in 65 patients (29.4%). The relative risk (RR) of a cardiovascular event in a patient with an ECG abnormality was 8.28 (95% confidence interval [CI], 3.36-20.42). Only hypertension (RR=2.29; 95% CI, 1.24-4.22) and age were significantly related to the occurrence of a cardiovascular event. Multiple regression analysis that included classical risk factors and ECG findings showed that an ECG abnormality was a significant independent predictor, with adjusted RR=5.95 (95% CI, 2.29-15.47).

Conclusions. The presence of an ECG abnormality can predict the occurrence of a future cardiovascular event in patients with DM2 more accurately than risk factors alone. This finding could be helpful in selecting subgroups of high-risk diabetic patients.

Key words: *Diabetes mellitus. Prognosis. Electrocardiography.*

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Valor pronóstico del electrocardiograma en pacientes con diabetes tipo 2 sin enfermedad cardiovascular conocida

Introducción y objetivos. El valor predictivo de las alteraciones del electrocardiograma no ha sido plenamente estudiado en la diabetes tipo 2 (DM2). Nuestro objetivo fue evaluar el valor pronóstico de las alteraciones del ECG en pacientes con DM2 sin enfermedad cardiovascular conocida.

Métodos. Se identificó 412 casos de DM2 en dos centros de salud de una misma población. Se incluyó en el estudio a 221, menores de 80 años sin enfermedad cardiovascular conocida. Se realizó un seguimiento con un ECG anual. Se analizaron los ECG mediante un sistema basado en el código de Minnesota. Se consideró puntos finales del seguimiento los eventos cardiovasculares definidos en el estudio de Framingham.

Resultados. El seguimiento medio (intervalo) fue de 5,9 (1,1-8,5) años. El 24,9% de los pacientes mostraba alteraciones en el ECG al inicio del estudio y el 44,3%, al final. Hubo eventos en 65 (29,4%) casos. El riesgo relativo (RR) de tener un evento con ECG anormal era de 8,28 (intervalo de confianza [IC] del 95%, 3,36-20,42). Sólo la hipertensión (RR = 2,29; IC del 95%, 1,24-4,22) y la edad mostraron relación significativa con los eventos. Un estudio de regresión múltiple que incluía los factores de riesgo clásicos y el ECG mostró que éste tenía un valor predictivo independiente, con RR ajustado = 5,95 (IC del 95%, 2,29-15,47).

Conclusiones. Las alteraciones del ECG pueden predecir la aparición de eventos cardiovasculares con mayor precisión que los factores de riesgo solos en los pacientes con DM2. Esto podría ser de interés para seleccionar subpoblaciones de diabéticos de mayor riesgo.

Palabras clave: *Diabetes mellitus. Pronóstico. Electrocardiografía.*

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ABBREVIATIONS

CI: confidence interval
DM2: type 2 diabetes mellitus
ECG: electrocardiogram

INTRODUCTION

Controversy exists concerning the role of the electrocardiogram (ECG) in predicting the cardiovascular risk in the general population.[1,2] Although an abnormal ECG has been shown to be associated with an increase in cardiovascular mortality in asymptomatic patients,[3-5] this increase may be so small compared to the influence of cardiovascular risk factors[6] that many authors cast doubt on whether the ECG should be used to evaluate the risk in the general population.[2,6,7] Populations with a high cardiovascular risk, however, may be an exception to this idea.[7] It has been suggested that in these cases the asymptomatic changes in the ECG may predict medium-term events more accurately than the traditional risk factors.[8] In this context, the usefulness of the ECG as a prognostic tool has been clearly shown in patients with hypertension and in patients with left ventricular hypertrophy.[9,10] It is also known that the combined evaluation of the ECG with another risk marker, microalbuminuria, improves the predictive value of the ECG in the general population.[11]

Type 2 diabetes mellitus (DM2) is an independent cardiovascular risk factor. DM2 is also associated with a high prevalence of ECG abnormalities, which have been found to be as high as 73%.[12] There seems to be no doubt that these abnormalities are more common in persons with diabetes than in persons without diabetes.[13,14] Although the prevalence of these abnormalities has been examined in numerous studies,[13-17] the prognostic value of these abnormalities has only been studied systematically in patients with impaired glucose tolerance,[16,17] and just more recently in populations of North American Indian tribes with DM2.[18,19] These were found to have an association between major ECG abnormalities and the risk of death. The aim of our study was to assess the prognostic value of ECG abnormalities in patients with DM2 without known cardiovascular disease, for both cardiovascular disease and death.

METHODS

The study, undertaken in the city of Alcalá de Henares, Madrid, Spain, was non randomized and included 2 primary health care centers and a total of 6 family physicians. All patients from the 2 care centers with a diagnosis of DM2 were enrolled in a care and follow-up protocol that included, among other things, an ECG at least once a year. The diagnosis of DM2 was made according to the definition of the National Diabetes Data Group,[20] accepted by the World Health Organization in 1985.[21] Briefly, these criteria were: *a)* in the case of symptoms of diabetes, glycemia >200 mg/dL at any time of the day or a baseline glycemia >140 mg/dL, and *b)* in the absence of symptoms, a baseline glycemia ≥140 mg/dL on 2 different days or a glycemia ≥200 mg/dL 2 h after an oral glucose tolerance test. No prospective search for cases was made with this test unless there was a clinical indication. The study was started in January 1994 and the follow-up data were collected up to June 2002.

Patients older than 80 years of age at the start of the study and those with known cardiovascular disease were excluded. A patient was considered to have cardiovascular disease if he or she had a previous diagnosis of angina, myocardial infarction, heart failure, stroke, or intermittent claudication. All the patients underwent a medical history and physical examination at the start of the study and during the follow-up, with special interest being paid to the search for symptoms of cardiovascular disease and examination of the peripheral pulses. In the event of signs or symptoms of the diseases mentioned, the patients were studied in order to confirm or reject the diagnosis, and only then were they included or excluded from the follow-up protocol.

The blood pressure was measured according to the recommendations of the Fifth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V),[22] current at the start of the study. Patients were considered to have hypertension when their systolic blood pressure was ≥140 mm Hg and their diastolic blood pressure was ≥90 mm Hg, after a minimum of 3 correct measurements.

Hypercholesterolemia was diagnosed if the total cholesterol was ≥250 mg/dL at 2 different measurements, in accordance with the criteria of the National Cholesterol Education Program - 2nd Adult Treatment Panel, current at the time the protocol was designed.[23]

The protocol included general measures for the pharmacologic management of the patients, though the medical treatment was not standardized.

An ECG was performed at the time of inclusion in the study and each year during the study period. The ECG study was done using a classification system based on the Minnesota code,[24] which was modified with the criteria of Cornell[25] for the criterion for hypertrophy, which has been endorsed by publications more than the simple voltage criteria included in the original coding. The ECG were analyzed by 2 family physicians and a cardiologist, following a training period. This training consisted of jointly analyzing 80 ECG taken at random from the health center records, using the Minnesota code as the reference and the opinion of the other 2 doctors. The 2 family physicians later individually analyzed each ECG blinded to the patient data. When the interpretations varied, a cardiologist analyzed the recording with them and a

consensus diagnosis was sought among the 3. A total of 1426 ECG were analyzed, with initial discordance in 756 (53%), higher than the 46% reported for expert cardiologists.[26]

Study outcome variables were considered to be cardiovascular events defined according to the Framingham study.[27] These included death of the patient, myocardial infarction, stable or unstable angina, heart failure, stroke, and intermittent claudication.

The extrahospital diagnosis of heart failure required compliance with the diagnostic criteria of the Framingham study,[28] which include signs, symptoms and criteria of response to diuretics, and classified as major or minor criteria. For the other end points, confirmation of the diagnosis was required by a physician of the corresponding specialty not involved in the study, using whatever studies were considered necessary. The data on death were obtained from the health center records and the death certificates or by interviewing relatives of the deceased when the former were not available or not sufficient.

The data were analyzed using the statistical package SPSS 11.0. Independent continuous variables were compared with the Student *t* test. Discrete variables were compared with Pearson's χ^2 test and estimation of the risk. Survival was analyzed with Cox regression analysis. The variables incorporated into this analysis were the traditional cardiovascular risk factors (age, sex, hypertension, hypercholesterolemia, and smoking), as these may act as confounding factors in the association between the abnormal ECG and the appearance of cardiovascular complications. The introduction of variables was done using Cox models with sequential adjustments. The hazard ratio (HR), as an approximation to the relative risk, was calculated to quantify the association. The follow-up time was measured in months, from the first ECG up to the time of the first event (or simultaneous events) or until closure of data collection if the patient remained event-free. A *P* value less than .05 was considered significant, and the estimations of risk were calculated with their 95% confidence intervals (CI).

RESULTS

A total of 412 cases of DM2 were recorded in the study population of 11 952 adults, giving a prevalence of known DM2 of 3.4% in the cohort. Of these 412 subjects, 63 were excluded because they were older than 80 years of age at the time of inclusion and another 75 patients, younger than 80 years of age, were excluded because they had already suffered a cardiovascular event. A further 53 subjects were either lost to follow-up or refused to continue. The remaining 221 subjects thus comprised the final study sample. The mean (standard deviation [SD]) age at inclusion was 64 (9.4) years, with 53% of the subjects being men. All except 2 were European of Mediterranean origin. The mean (interval) follow-up time was 5.9 (1.1-8.5) years.

At the start of the study, 132 (59.7%) patients had hypertension; 122 (55.2%), had hypercholesterolemia; 82 (37.1%) were either current smokers or had quit in the previous 2 years, and 95 women (91.3% of the women) were post-menopausal. During the follow-up period, 65 (29.4%) patients had a total of 103 cardiovascular events, with a mean incidence of 5 per 100 patients per year of follow-up. The types of events and their distribution according to sex are shown in Table 1. The number of complications exceeds the number of patients because many of them had various simultaneous events, for instance, heart failure due to myocardial infarction. Heart failure was more common in women and intermittent claudication was more common in the men, though no differences were found between the sexes when the events were analyzed together. Figure 1 shows the distribution of all the events according to the presence or absence of risk factors. The patients with hypertension had more complications than those without hypertension. The affected patients were significantly older (69.1 [7.9] vs 63.5 [10.2] years; *P*=.0001). No significant differences were found for the presence or absence of hypercholesterolemia, or smoking when the events were considered as a whole, but both angina and myocardial infarction were more frequent in the patients with total cholesterol levels >250 mg/dL (28 and 6 cases, respectively; *P*<.05).

TABLE 1. **Type of Event and Distribution According to Sex**

	Men, n (%)	Women, n (%)	*P*
Cases with 1 or more events	32 (27.4)	33 (31.7)	NS
Cardiovascular death	7 (6)	8 (7.7)	NS
Myocardial infarction	8 (6.8)	4 (3.8)	NS
Angina	11 (9.4)	11 (10.6)	NS
Heart failure	5 (4.3)	14 (13.5)	.02
Stroke	14 (12)	13 (12.5)	NS
Intermittent claudication	7 (6)	1 (1)	<.05
Total events[a]	52	51	

[a]The total number of events exceeds the number of patients who had events because some patients had more than one event at the same time.

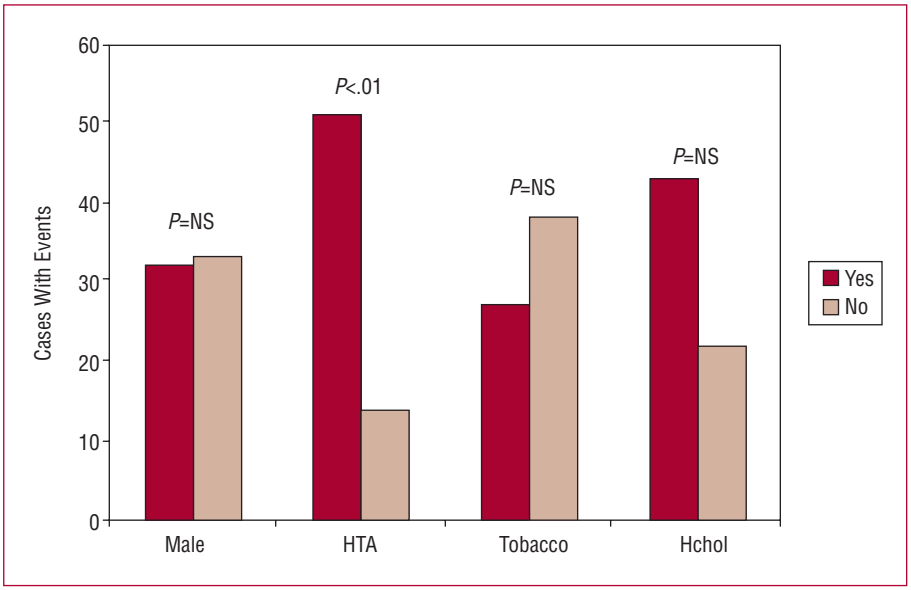

Figure 1. Distribution of the number of cases with events, according to the cardiovascular risk factors. Hchol indicates hypercholesterolemia; HTA, hypertension; NS, not significant; Tobacco, active smoker.

TABLE 2. **Cardiovascular Events in Patients With and Without Electrocardiographic Abnormalities**[a]

	Abnormal ECG, n (%)	Normal ECG, n (%)	*P*
Cardiovascular events	55 (56.1)	10 (8.1)	<.01
Cardiovascular death	13 (13.3)	2 (1.6)	<.01
Myocardial infarction	9 (9.2)	3 (2.4)	.03
Angina	18 (18.4)	4 (3.3)	<.01
Heart failure	17 (17.3)	2 (1.6)	<.01
Stroke	22 (22.4)	5 (4.1)	<.01
Intermittent claudication	7 (7.1)	1 (0.8)	.01

[a]ECG indicates electrocardiogram.

TABLE 3. **Estimation of the Crude Unadjusted Risk Associated With Each Factor**[a]

	RR (95% CI)	*P*
Hypercholesterolemia	2.21 (0.98-4.97)	NS
Hypertension	2.29 (1.24-4.22)	<.01
Smoking	1.21 (0.58-2.55)	NS
Male sex	1.43 (0.70-2.94)	NS
Age	1.05 (1.01-1.10)	.01
Abnormal ECG	8.28 (3.36-20.42)	<.01

[a]CI indicates confidence interval; NS, not significant; RR, relative risk.

TABLE 4. **Multivariate Analysis, Adjusted for Hypertension, Hypercholesterolemia, Sex, and Smoking, of the Association Between Electrocardiographic Abnormalities, Age, and the Development of Cardiovascular Events**[a]

	Coefficient	SE	*P*	RR	95% CI
Age	0.045	0.022	.04	1.46	1-1.09
ECG	1.784	0.487	<.01	5.95	2.29-15.47

[a]ECG indicates electrocardiographic abnormalities; SE, standard error; CI, confidence interval; RR, relative risk.

At their inclusion in the follow-up, 55 (24.9%) patients had an abnormal ECG with no other evidence of cardiovascular disease. At the end of the study 98 (44.3%) patients had an abnormal ECG. The ECG changed or became abnormal at a rate of 4.4% per year.

The patients with ECG abnormalities had more cardiovascular events than those who had a normal ECG (Table 2). The crude relative risk (RR) of an event in a patient with an abnormal ECG was 8.28 (95% CI, 3.36-20.42), much higher than the risk due to hypertension, the most significant of the traditional risk factors in our sample (RR=2.29; 95% CI, 1.24-4.22). Table 3 shows the unadjusted risk for each risk factor. Only age, hypertension, and ECG abnormalities reached statistical significance. Table 4 shows the results of the multiple regression study, which included age, hypertension, sex, hypercholesterolemia, smoking, and ECG abnormalities. As can be seen in the Table, both ECG abnormalities and age were independent predictive factors.

Certain ECG abnormalities were analyzed separately. Their frequency is shown in Table 5. Of the 24 patients with electrocardiographic data of left ventricular hypertrophy, 20 had hypertension. Other abnormalities, such as left bundle branch block, were not analyzed due to their low frequency (2 cases, both with events). For the same reason no multivariate analysis was made of their individual risk. The presence of left ventricular hypertrophy, abnormal repolarization, pathologic Q waves and/or atrial fibrillation had a specificity >80% for the prediction of a cardiovascular event. Of these, repolarization abnormalities were the most sensitive finding (55%) and atrial fibrillation the most specific (99%). Overall, the presence of any ECG disorder was highly sensitive (87%) though less specific (64%) for the prediction of events (Table 5).

DISCUSSION

This study showed that patients with DM2 without clinical cardiovascular disease who have an abnormal ECG have an increased risk for cardiovascular events in the medium term. The association found between the ECG findings and the risk was closer than that for the traditional risk factors, a finding that supports the proposal of Cuples et al.[8]

The findings of the study are in agreement with those reported for populations with a high cardiovascular risk, such as persons with hypertension and patients with left ventricular hypertrophy.[9,10] They also coincide with the association between mortality and ECG abnormalities found in American Indians with DM2.[18,19] Not only do the findings of this study conform to the findings of the studies mentioned above, but unlike these, our study examined cardiovascular death and disease and not just death alone. Additionally, the study excluded patients with known cardiovascular disease, in whom the prognostic value of an ECG is of less importance because the disease that is already present represents a very much higher risk. The study is also related with the findings of the HOPE study,[29] which found that the use of ramipril in patients with an abnormal ECG conferred a greater benefit.

Several explanations may account for our results. The cause of ECG abnormalities in patients with DM2 extends far beyond the association evident with ischemic heart disease.[30] Repolarization disorders are not necessarily due to ischemia. Left ventricular hypertrophy is very common in diabetic patients, both with and without accompanying hypertension,[31] and it often causes repolarization disorders without necessarily producing an increase in voltage, so that it is often under-diagnosed with ECG. Hypertrophy due to hypertension would explain an important part of the risk in these patients and the ECG abnormalities. In this case, an echocardiogram could have provided interesting data in this study. We must assume, therefore, that the changes in the ECG and the increase in risk are due to combined causes and not just to the diabetes itself. Diabetic dysautonomy and diabetic heart disease are equal causes of ECG abnormalities,[32] and the metabolic disorders associated with diabetes may also change the ECG temporarily.[33] All these conditions, and not just ischemic heart disease, are associated with an increase in cardiovascular disease. To this extent, the fact that we did not select just those disorders that indicate ischemic heart disease, unlike what others have done,[18,19] seems to make pathophysiologic sense. The ECG would reflect microvascular, tissue and even metabolic damage due to multiple factors, and it would enable detection of those patients at greatest risk.

The increased risk conferred by diabetes per se may attenuate the importance of the influence of the other risk factors. This is what happened in our sample with smoking and hypercholesterolemia, whereas hypertension and age maintained their statistical influence on the risk for events. Women with DM2 are reported to have a similar cardiovascular risk to men with DM2.[34] Hypercholesterolemia was associated with the presence of angina and myocardial infarction, but not with total events. This result, coherent with the hypothesis of a different influence of different risk factors with different types of events, indicates that with a larger sample the associations might have been more obvious. Thus, in our case, this lack of association may be due to the small size of the sample studied. Additionally, the sample size impeded a multivariate analysis of the association between each type of ECG abnormality and the various complications. However, we feel that, even though the sample size was limited, the study remains of interest: once the statistical effect of certain known classic risk factors was lost, the ECG proved to be a good tool to select those patients with diabetes at greatest risk.

The sample was not population-based nor was it randomly selected, and neither was it selected to determine the prevalence of DM2 or ECG abnormalities in patients with diabetes. Our results, therefore, are merely orientational. The presence of pathologic Q waves (without an otherwise demonstrated infarction) or atrial fibrillation could, by themselves, have been considered events. They were included in order to maintain similarity with the Framingham study, whose definitions we adopted. The same reason led to the exclusion of persons aged 80 years or over. The cut-off points to consider hypertension and

TABLE 5. **Relative Risk (Unadjusted) and Diagnostic Value of Different Types of Electrocardiographic Disorders[a]**

	Cases, n (%)	RR (95% CI)	*P*	Sensitivity, %	Specificity, %
LVH	24 (8.1)	3.5 (2-6.2)	<.01	24	95
Abnormal repolarization	61 (24.4)	3.8 (2.2-6.7)	<.01	55	82
Pathologic Q waves	10 (4.5)	4 (2.2-7.2)	<.01	16	98
Atrial fibrillation	7 (3.2)	4.6 (2.2-8.1)	<.01	13	99
Any disorder	98 (44.3)	8.3 (3.4-20.4)	<.01	87	64

[a]Any disorder indicates any disorder noticeable on ECG; LVH, left ventricular hypertrophy; CI, confidence interval; RR, relative risk.
The sum of all the abnormalities considered in the table exceeds the number of patients shown because most patients had several different forms at the same time.

hypercholesterolemia have changed a lot since the protocol for this study was designed. With current criteria, the classification of the patients according to risk factors would have been different and would have included patients with hypertension and hypercholesterolemia and persons with lower blood pressure and cholesterol figures. The definition, too, of diabetes changed during the study follow-up period. Although this is a clear limitation of the study, it has been imposed on us by the changes in diagnostic criteria that occur from time to time. We believe that these facts do not annul the value of our results. If the current criteria were applied to the same population, with much lower limits, the risk factor groups would have included persons with a theoretically lower risk, and the association between the traditional risk factors and the events would have been weaker. However, these changes would not affect the value of an abnormal ECG. ECG, therefore, could be a useful, cheap and immediate tool to determine the increase in risk in patients with known diabetes for whom doubt exists concerning their overall risk, either because they have borderline values for other risk factors, or because of inadequate or incomplete follow-up.

CONCLUSIONS

In patients with DM2 without known cardiovascular disease, the appearance of ECG abnormalities may be a tool to detect those cases with a higher risk of future cardiovascular events, in addition to the presence of other risk factors. This could be of practical interest to select populations in whom prevention should be more aggressive.

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