Risk Factors Other Than Hyperglycemia in Diabetic Macrovascular Disease

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A five-year prospective follow-up study was done on 10,000 adult males in Israel. The end-points of diabetes mellitus—clinical and unrecognized myocardial infarction, angina pectoris, sudden death, and hypertension—were examined. The incidence rates rise with age and vary significantly by areas of birth, with the Middle Eastern and North African subjects having the highest incidence of diabetes but the lowest cardiovascular rates. A developmental medical model based on a historical-societal perspective is proposed to explain these findings. The major factors found on multivariate analysis in the development of diabetes mellitus are compared with those of the other cardiovascular end-points mentioned above. The similarities and differences between these risk factors are discussed, and I conclude that the prevention or alleviation of diabetic macrovascular disease needs a multifactorial approach against the major risk factors of the macrovascular complications as well as those related to diabetes, in the individual, family, and community. DIABETES CARE 2: 77–84, MARCH–APRIL 1979.

Research in diabetes mellitus was intensified following the discovery and production of insulin by Banting and Best in 1921, but the work over the last 50 yr has still not elucidated some of the major problems associated with this condition. One area of mystery is the fact that the vast majority of individuals with diabetes, of all types, die from cardiovascular complications (or associations), but the mechanisms and variables of the diabetic state (or its treatment) that lead to cardiovascular manifestations are still not clear.

Some of this lack of clarity is due to different definitions, classifications, and methodology, which this conference has and will deal with. In addition, it is now obvious that there are real and substantial geographic and sociocultural differences in the prevalence and incidence of both diabetes and its cardiovascular manifestations.

The international representation of the participants of this conference emphasizes the importance of studying these differences in order to help us try to elucidate the unsolved problems.

It is with this objective that I shall describe our work in Israel and present some of the findings which might reinforce or differ from those from other places. I will only highlight certain points of interest and will not attempt a comprehensive look at the subject.

MATERIALS AND METHODS

The study population consisted of tenured government and municipal male employees aged 40 and over at the onset of the study. These 24,300 men were grouped in six large areas of birth, and a varying sampling ratio was chosen for each area (Table 1). All the sample members living in or near the three largest cities (Jerusalem, Haifa, and Tel-Aviv) were then invited to participate in the initial examination. A total of 10,232 men (86.2%) responded, and two further comprehensive examinations were performed at intervals of 3 and 5 yr.[1] Parallel to this, an efficient monitoring system kept the whole group under surveillance for serious illness and deaths through the 5-yr period.[2] At the final examination, 98% of those still living were reexamined, while the 100% mortality follow-up was extended for a total of 7 yr. In other words, the morbidity follow-up was for 5 yr or approximately 50,000 person-years of observation, while the mortality follow-up of 7 yr gave approximately 70,000 person-years of observation.

TABLE 1
Basis for sample selection and response

1.	Males only	
2.	Aged 40 and over at beginning of study	
3.	Area of birth:	Varying sampling ratio:
	Eastern Europe	1 in 4
	Central Europe	5 in 6
	Southeast Europe	5 in 7
	Israel	1 in 1
	Middle East	1 in 1
	North Africa	1 in 1
4.	Cities of work: Jerusalem, Haifa, Tel-Aviv	
5.	Response:	
	Basic population	24,300
	Chosen	14,283
	Ineligible	2407
	Invited sample	11,876
	Participated in first examination	10,232 (86.2%)
	Records used in analysis	10,059

At the initial examination, all the dependent variables or disease conditions identified were included in the prevalence figures for that condition, and all those without signs of the condition were regarded as being at risk for the prospective follow-up. Any subject developing one of these conditions during the follow-up period or found at the final examination was classified as an incidence case. Efficient control and supervisory procedures were carried out throughout and have been described.[3] The disease conditions identified, with which we will deal today, are clinical myocardial infarction, unrecognized myocardial infarction, angina pectoris, sudden death, hypertension, and diabetes. The specific details for each of these conditions have been described fully elsewhere and I shall not repeat them here.[4–9] A list of over 100 independent variables examined are given in the Appendix of reference 4.

Statistical analysis[10–12] involved the following procedure: (a) comparison of incidence rates observed in percentiles (deciles and tertiles) of each of different variables. For ordinal and interval variables, a Student's t test for the "slope" was used. For the nonordinal variables a similar significance chi-square test was used; and (b) a multivariate analysis using iterative logistic regression, which estimates the probability of the event in the 5-yr period. Multiple risk coefficients, reflecting change in log odds to develop, for example, myocardial infarction associated with the shifting of levels for the particular variables, are given. Details of the procedure are stated in a previous publication.[6] To select the variables in the multivariate analysis, a stepwise linear regression was run with the dependent variable set at 0 to 1, respectively, for the absence or presence of a first myocardial infarction (during the 5-yr follow-up). The set of "independent variables" included all variables with a significant slope for the incidence of either unrecognized or total myocardial infarction at the simple comparison 0.05 level. Variables still significant in this context were used in the logistic regression procedure described above.

RESULTS AND DISCUSSION

The average annual age-area adjusted incidence rates and the variations between the birth areas, for diabetes, clinical and unrecognized myocardial infarction, angina pectoris, and hypertension are shown in Table 2. In all cases, the incidence rates rise with age. Without considering variations in definition and methodology, it can be said that these figures are comparable to the rates of many European and North American studies. The birth areas with the highest and lowest incidence rates for these conditions are shown in Table 3. It is interesting to note that those subjects born in the Middle East and North Africa have the highest rates of diabetes but are in the lowest or next to lowest category for all the other conditions. By contrast, the European born have the lowest diabetic rate but are in the highest categories for all the others. The differences between these categories reach statistical significance in all cases. How can we explain this difference between the subjects born in relatively underdeveloped countries to those from Europe?

An attractive hypothesis would be an extension of Neel's "thrifty genotype" theory.[13] The subjects from the underdeveloped countries, on immigrating to Israel, were faced with an environment in which there was better nutrition (more food available) together with a work and living situation which demanded less physical activity than they were accustomed to. (In parenthesis, one can state that the change in the weight and height of the infants and youths in one or two generations has been

TABLE 2
Incidence of cardiovascular and related manifestations in 10,000 adult males (5-yr prospective study)

Condition	Average annual adjusted incidence rate/1000	Variations between birth areas
Clinical myocardial infarction	5.3	3.6–7.1
Unrecognized myocardial infarction	3.6	3.0–4.6
All myocardial infarction	8.7	7.4–10.0
Angina pectoris	7.2	3.8–11.2
Hypertension	10.0	6.0–15.0
Diabetes	8.0	5.6–11.2

TABLE 3
Highest and lowest incidence by area of birth

Condition	Highest	Lowest
Clinical myocardial infarction	Central Europe	Middle East/ N. Africa
Unrecognized myocardial infarction	Southeastern Europe	N. Africa/ Central Europe
Angina pectoris	Southeastern Europe	Middle East
Hypertension	Southeastern Europe	N. Africa/Israel
Diabetes	Middle East	Eastern and Central Europe

Subjects born in the Middle East have the lowest or near the lowest incidence for all conditions, except for diabetes, for which they have the highest incidence.

TABLE 4
Developmental cycle of diabetes and cardiovascular conditions in populations whose living conditions "improve"

Stage I	Decrease of infectious diseases
Stage II	Increase of diabetes (second generation) Some increase of cardiovascular risk factors No increase of cardiovascular morbidity
Stage III	High diabetic rate Increased cardiovascular morbidity
Stage IV	Diabetic rates diminishing High cardiovascular rates
Stage V	Lower rates of diabetes and cardiovascular conditions (adjusted phase)

remarkable.) This allowed their "thrifty genotype" to come to the fore, and the numbers of diabetic patients rose. Another point to remember is that this diabetic "outgrowth" takes a relatively short time, whereas the changes associated with the development of atherosclerosis and its various manifestations occurs over a more prolonged period. If this is acceptable, we can hypothesize a sequence of interrelated developmental stages based on a historical-societal perspective as shown in Table 4.

The above developmental cycle of diabetes and cardiovascular conditions not only could apply to groups of people immigrating to more developed countries but also could help explain the effect of internal migrations in certain countries (e.g. the increase of diabetes in blacks coming from the rural South to the industrial North in the U.S.A.) as well as the effect on stable populations whose areas become more urbanized and industrialized, as is happening in many parts of the southern sunbelt in the U. S. and other parts of the world. A fascinating example of this is the small Pacific island of Nauru, where the life-style of the indigenous population has been revolutionized by the rich deposits of phosphates discovered (see Zimmet's paper in the proceedings of this conference).

In keeping with this hypothesis, it is interesting to note the generational differences in incidence rates. The general pattern of the cardiovascular conditions shows a slight rise in the first local-born generation as compared to the immigrants, with a decrease in the second generation. With diabetes, however, there is a rise in the second generation (Figure 1). These differences are not statistically significant, but the inverse pattern of diabetes as compared to the rest should be noted.

Clinical work is still very much geared to normal and abnormal values with defined cut-off points, despite the fact that most epidemiologic studies show a continuous relationship between risk factors and the end point. This occurs with cholesterol, blood pressure, and glucose values (Table 5) as related to myocardial infarction. I wonder how these epidemiologic findings can be translated into meaningful clinical values so that hospital laboratories and physicians will not classify results as normal or abnormal.

At the first survey examination, there were 270 subjects with a history of diabetes that we confirmed as being compatible with our criteria and who were classified as having "previously diagnosed" diabetes. In addition, another 209 subjects were diagnosed as having diabetes for the first time by the survey examination and were labeled as having "newly diagnosed diabetes." The latter constituted 43.6% of all those diagnosed at the prevalence survey (Table 6). Note that about two-thirds of the European-born subjects were aware of their diabetes, whereas it was known to only about half of the others. This could be due to a differential use of medical services, but as medical services were freely available to all our study population and studies have not shown any preponderance of

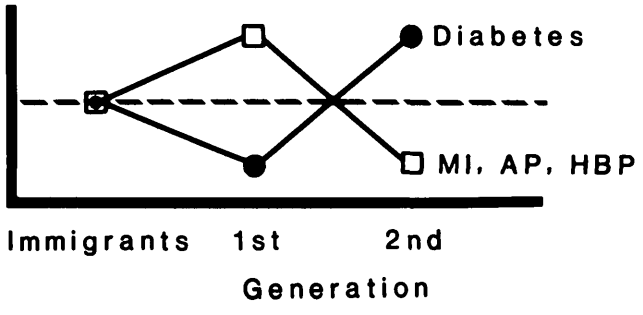


FIG. 1. Generational differences in incidence. MI, myocardial infarction; AP, angina pectoris; HBP, high blood pressure.

TABLE 5
Glucose and 5-yr incidence of myocardial infarction

Casual glucose (mg/dl):	−129	130–159	160+
No. at risk	8513	184	221
Adjusted rate/1000	44	70	90

European-born physician contacts, this variation may be due primarily to the European-born having diabetes of a more severe nature which would lead to more frequent and earlier diagnoses being made.

Having these two groups of individuals with diabetes (previously diagnosed and newly diagnosed) allowed us to follow and compare their differences in morbidity and mortality over the next 5 yr in order to determine the effect of the duration of the disease on the cardiovascular end-points. The logical thing would have been to analyze the Europeans and others separately, but unfortunately, the numbers often became too small for any meaningful conclusions to be drawn, so we looked at the two groups of previously and newly diagnosed, irrespective of their birth place.

The diabetic individuals in the study had twice the mortality rate from all causes than the nondiabetic individuals,[14–16] with a little over 50% of this mortality being due to myocardial infarction and sudden death (Table 7). Those with diabetes of longer duration (previously diagnosed) had more deaths from all causes than the newly diagnosed ones.[17] The deaths from myocardial infarction, however, did not appear to be related to the duration of the diabetes, whereas in sudden deaths the duration might play a role, although the small numbers make conclusions difficult.

In respect to certain morbidity states (Table 8), the presence of diabetes did not increase the rate of left ventricular hypertrophy or of hypertension (some authors have reported similar and others conflicting results[18–20]), whereas it did increase the rates for myocardial infarction, angina pectoris, and especially intermittent claudication. In none of these conditions except angina pectoris was there any difference between the previously and newly diagnosed diabetic groups. Angina pectoris seems to be associated with duration of the diabetic state. Clinically, Root et al. reported similar associations with angina pectoris.[21] The explanation for this possible association between duration and angina pectoris/sudden death, but not the others, eludes me.

TABLE 6
Percentage with newly diagnosed diabetes at first survey examination

Area of birth	Percent of newly diagnosed
Europe	
Eastern	32.6
Central	36.5
Southeastern	27.5
Israel	47.8
Middle East	44.8
North Africa	53.3
All countries	43.6

The age-adjusted mean values for a number of risk factors as related to previously and newly diagnosed diabetes are shown in Table 9. With the exception of uric acid, the other risk factors are all raised in those with diabetes as compared to those without diabetes (total population minus those with diabetes), but they are lower in the previously diagnosed than the newly diagnosed group. This unexpected finding is due, we hope, to the results of medical management of the previously diagnosed group with a consequent reduction of weight, blood pressure, and cholesterol levels.

As regards uric acid, we have reported a number of interesting points.[22] First, there is a direct significant association between serum uric acid level and the development of diabetes. Once the state of hyperglycemia and glucosuria supervenes, however, there is a drop in serum uric acid level, and this inverse relationship becomes stronger, the longer the diabetes exists (Table 9).[23] Follow-up work by my colleague, Joseph Herman, has led us to the belief that "in persons with hyperglycemia and glucosuria, there seems to be a competitive inhibition of uric acid reabsorption in the proximal tubules by glucose. The increased uric acid excretion arising in this way would cause a gradual decline in serum uric acid."[23]

Over the last 5 yr or more, we have published a number of articles reporting the variables (risk factors) associated with the incidence of the major manifestations of ischemic heart disease and related conditions as exhibited by multivariate analysis. We have also produced a manual (as was done from the Framingham Study[24]) showing the probability of developing these conditions within 5 yr at different levels and combinations of the risk factors.[25]

These multivariate analyses show that diabetes is a significant independent risk factor in the production of clinical myocardial infarction, angina pectoris, and sudden death. To our surprise, however, diabetes was not a significant factor in the multivariate analysis of unrecognized myocardial infarction or of hypertension, even though it had been in the univariate and bivariate context. To try to elucidate further some of this puzzle, let us look at the risk factors in the development of diabetes mellitus and compare them with the significant factors associated with the major cardiovascular conditions.

TABLE 7
Mortality ratios in diabetes (5-yr follow-up)

Cause of death	Diabetes								
	Previously diagnosed (n = 270)			Newly diagnosed (n = 209)			All diabetes (n = 479)		
	Observed	Exp.*	O/E	Observed	Exp.	O/E	Observed	Exp.	O/E
Myocardial infarction	12	3.5	3.4	8	2.4	3.4	20	5.9	3.4
Sudden death (<1 h)	8	2.2	3.6	1	1.6	0.6	9	3.8	2.4
All causes	40	17.1	2.3	16	11.4	1.4	56	28.5	2.0

* Expected rates based on nondiabetic population.

The left-hand column of Table 10 shows the significant variables related to diabetes. The major significant variables were age and overweight with standardized beta coefficients of 0.31 and 0.36, respectively. Peripheral vascular disease (0.18) and total serum cholesterol (0.15) were also significant at the $P < 0.01$ level, as were European-born and level of education, which both had negative correlations. Blood pressure and uric acid were significant at $P < 0.05$ level, while hemoglobin (but not hematocrit) was significantly associated ($P < 0.01$) with the 50–59 yr age group only. Notable nonsignificant variables included smoking, anxiety, psychosocial problems, and dietary constituents. This result is in agreement with Mirsky's statement that the probability is that "diabetes mellitus in man is a complex of at least two related syndromes. One . . . attributable to a defect in the metabolism of foodstuff . . . due to a decreased availability of insulin to the cells. The other is characterized by signs and symptoms of vascular damage attributable to an independent defect in the metabolism of the vessels. Either syndrome may precede the other, may occur without the other, or both may occur together. It is quite possible, however, that one may aggravate the other."[26]

Comparing the diabetic risk factors of Table 10 with those related to the other end-points in the table highlights the following points:

1. *Age and blood pressure* are the only two variables that are consistently and significantly related to all end-points.[27]

2. *Total serum cholesterol* is directly associated with all conditions except unrecognized myocardial infarction. *Cholesterol in high density lipoprotein* is inversely related to these same end-points, but the relationship becomes stronger than total serum cholesterol in the higher age groups (55 or older). In addition, HDL is related to obesity and physical activity as well as perhaps being important in the process of aging.[28]

3. *Overweight*[29] is significantly associated with diabetes and hypertension, but not with the others. However, in the stepwise regression analysis, it was seen that overweight was related to myocardial infarction and angina pectoris (Table 11) but fell away as soon as hypertension was added. In other words, it seems probable that the effect of over-

TABLE 8
Morbidity ratios in diabetes (5-yr follow-up)

Type of morbidity	Diabetes											
	Previously diagnosed				Newly diagnosed				All diabetes			
	No.	Observed	Exp.*	O/E	No.	Observed	Exp.	O/E	No.	Observed	Exp.	O/E
MI by ECG	245	23	15.4	1.5	195	15	11.1	1.4	440	38	26.5	1.4
AP only	181	18	5.6	3.2	166	3	5.0	0.6	347	21	10.6	2.0
Hypertension	118	5	5.3	1.0	75	4	3.1	1.3	193	9	8.4	1.1
IC	221	20	9.3	2.2	179	17	7.1	2.3	400	37	16.4	2.3
LVH	212	19	20.2	0.9	173	15	15.7	0.9	385	34	35.9	1.0

AP, angina pectoris; ECG, electrocardiogram; IC, intermittent claudication; LVH, left ventricular hypertrophy; MI, myocardial infarction.
* Expected numbers based on nondiabetic population.

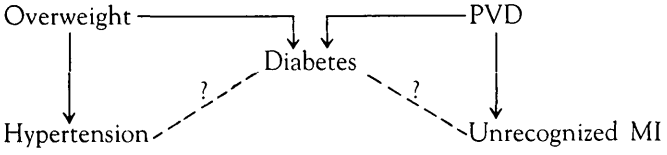
TABLE 9
Values of selected risk factors in diabetes (age-adjusted mean values)

	Previously diagnosed	Newly diagnosed	Total population
Cholesterol (mg/100 ml)	217	220	209
Systolic blood pressure (mm Hg)	138	146	135
Diastolic blood pressure (mm Hg)	84	87	84
Wt/ht^2	2.61	2.70	2.57
Uric acid	4.21	4.56	4.75

weight on the heart is mediated through its effect on blood pressure which in turn affects the heart and blood vessels.

4. *Peripheral vascular disease*, for so long regarded only as a complication of diabetes, can and does precede the glucose imbalance and is significantly associated with the incidence of diabetes as well as with unrecognized myocardial infarction.

An interesting point is that, while overweight and peripheral vascular disease are two major factors in the development of diabetes, and overweight itself is related to hypertension and peripheral vascular disease (PVD) to unrecognized myocardial infarction (MI), diabetes is not related to the latter two end-points.



5. *Uric acid*, although only related to diabetes, is present in many of the final analyses of the other end-points but tends to fall below the significant level. I would not be surprised if, in the future, a more important role for uric acid is discovered.[30–32]

6. *Birthplace* has been discussed previously.

7. *Education*—it was not too many years ago that myocardial infarction, angina pectoris, hypertension, and diabetes were associated with higher educational groups, but as the habits, behavior, and life-style of the latter changed (i.e., decreased smoking, more exercise, leaner stature, changed dietary patterns, etc.), so did the association with education. Presently, high diabetic rates, hypertension, obesity, and high total cholesterol levels are associated with the lower socioeconomic educated groups. This U.S.A. pattern is being repeated in other countries and cultures.

8. *Hemoglobin* and hematocrit are highly correlated with each other, so when there is a significant association as, for example, with sudden death, they were both related to the end-point. It was interesting, therefore, to see that hemoglobin, but not hematocrit, was related to diabetes in the 50–59 yr age group. Was this a portent of the recent finding of the importance of glycosylated hemoglobin (HbA_{1C})?[33]

9. *Blood group* associations are shown in Table 12. These were the only genetic markers we measured directly, but there is no one group common to all, although the A_1 and Kidd negative (Jk^{a-}) genes might be worthy of further study. In this population sample, there were so many parents and siblings who perished from unnatural causes

TABLE 10
Significantly associated risk factors (multivariate analyses) with 5-yr incidences

Diabetes	Clinical MI	Unrecognized MI	Angina pectoris	Hypertension	Sudden death*
X	Diabetes	—	Diabetes	—	Diabetes
Age	Age	Age	Age	Age	Age
Blood pressure	BP	BP	BP	(BP)	BP
Serum cholesterol	CHO	—	CHO	CHO	CHO
Peripheral vascular disease	—	PVD	—	—	—
Overweight	—	—	—	Overweight	—
Uric acid	—	—	—	—	—
Education (nc)	—	—	—	—	—
Hemoglobin (50–59)	—	—	—	—	Hb and Hct
—	Smoking	Smoking	—	Smoking	Smoking
—	AP	—	X	—	AP
—	—	ECG	ECG	—	ECG
—	—	—	Anxiety	—	Anxiety
—	—	—	Psychosoc. problems	—	—

Physical activity not included in five-year analysis.
For incidence by area of birth and by blood group, see Tables 3 and 12, respectively. nc, negative correlation. Other abbreviations, see footnote to Table 8.
* Sudden death analyses not final.

TABLE 11
Association of overweight with 5-yr incidence rates/1000

Weight/height²	Diabetes	Hypertension	MI	AP
Lowest tertile	23	29	38	35
Middle tertile	38	51	40	36
Highest tertile	58	95	49	42

TABLE 12
Highest blood group* association

Diabetes	AB
Serum cholesterol	A_1K+
All myocardial infarction	A_1BJk^{a-}
Angina pectoris	A_1BJk^{a-}
Hypertension	A_1Jk^{a-}

Jk^{a-} = Kidd negative.
* The blood groups tested were: ABO, Rh, MN, Kell, Duffy, and Kidd.

like wars, concentration camps, etc., that *family history* could not be used as a valid variable.

10. *Smoking* is not significantly related to the development of diabetes but is such a vital factor in the production of cardiovascular morbidity and mortality that there is no doubt in my mind that it should be regarded as a high risk factor in diabetic macrovascular disease.

11. *Psychosocial problems, anxiety, and support systems*[34–38]—the importance of these areas in clinical everyday practice is of the highest order, and the effects of acute stress on patients' blood sugar is well-known. Thus, it was a little disappointing to find that these variables did not contribute significantly to the development of diabetes. We did, however, find some exciting evidence of their relationship to angina pectoris[5] and to a lesser extent, with sudden death, so that these must be taken into account in considering macrovascular complications.

12. *Diet*—much to the irritation of some of my peers and to our own disappointment, we were, despite intensive efforts, unable to find a significant association, on an individual subject basis, between any of the dietary variables (*note*: salt intake was not measured) and diabetes and/or the other cardiovascular end-points; this, despite having an "ideal" heterogeneous population group with large variations of dietary intake.[39] Our conclusion is that we found no evidence that diet is a major factor in the development of cardiovascular conditions among the 10,000 adult males we investigated. It is, however, important to reduce total calories owing to the contribution of overweight.

13. *Physical activity*. Our measures of physical activity were rather gross and the follow-up was only accomplished for a 3-yr period. In the patterns displayed, there was a definite indication that a great deal of physical activity was associated with a decrease of myocardial infarcts.[37]

14. *Effect of treatment*. A factor which we did not measure, but which is of concern to diabetic patients and their physicians, is the effect of treatment or quality control on the incidence of macrovascular disease.

Where does this lead us? If we were hoping to find one or two major "causes" of macrovascular disease among individuals with diabetes, we were guilty of wishful thinking. Macrovascular disease is a group of conditions, each of which has a multifactorial epidemiologic picture, so unless we find the elusive "breakthrough," we should attack the problem by counteracting as many of the multiple factors as possible, in the individual, family,[37] and community.[35,36,38,40]

These factors are, I submit, those related to the development of diabetes (left column in Table 10) plus other factors related to the macrovascular complications (other columns in Table 10) and not necessarily directly to diabetes. These additional factors include cigarette smoking, reduction of anxiety, adjustment to psychosocial problems, and the improvement of social support systems.

Therefore, the risk factors associated with the development of diabetes and its macrovascular complications are, in this study population: age, overweight, peripheral vascular disease, blood pressure, serum cholesterol (total and high density lipoprotein), uric acid, birthplace (Middle East and North Africa), education (low), hemoglobin, smoking, anxiety, severe psychosocial problems, and lack of social support.

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