SPECIAL ARTICLE

Hyperglycemia

A Risk Factor in Coronary Heart Disease

By Frederick H. Epstein, M.D.

SUMMARY

This review article deals with the relation between hyperglycemia and myocardial infarction as observed after recovery from the acute attack or, to the extent that such data are available, antedating it. Hyperglycemia must be added to the various forms of hyperlipemia, positive caloric balance, hypertension, smoking, and others as a risk factor toward the development of manifest atherosclerosis. It remains to be established to what extent hyperglycemia, as one of multiple predisposing influences, is a predictive indicator in its own right. One part of this answer must come from prospective, epidemiological studies, the other from investigations of the interrelationships between lipid and carbohydrate metabolism in the different forms of hyperlipemia and the mechanisms by which hyperglycemia is produced.

Additional Indexing Words:
Atherosclerosis  Diabetes  Glucose tolerance  Lipids
Triglycerides  Cholesterol  Metabolism  Nutrition
Epidemiology  Myocardial infarction  Hyperinsulinism

It has been recognized for more than 30 years that diabetes predisposes to the various manifestations of atherosclerosis.1,2 A link between carbohydrate and lipid metabolism has also been known for a long time, as exemplified by the well-known saying attributed to Rosenfeld,3,4 that fats burn in the flame of carbohydrates. In the light of modern knowledge, the pathways of glucose and fatty acid synthesis and breakdown are linked by acetyl coenzyme A. When Gurin5 reviewed these interrelationships, Kendall6 stated in the discussion that the diagram used to illustrate the biochemical defect in diabetes was just as applicable for a discussion of artherosclerosis since both may be simply two manifestations of the same metabolic disease.

In this report, the term "hyperglycemia" is used in a broad sense, to include not only frank, clinically manifest diabetes but lesser degrees of impaired glucose tolerance. It is likely that glucose tolerance, like serum cholesterol or blood pressure level, represents a multifactorially determined, continuous variable so that the decision where "normality" ends and "abnormality" begins has to be made arbitrarily. The term "hyperglycemia," being shorter and less awkward than the more desirable expression "impaired glucose tolerance," seems perfectly acceptable as long

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as it is understood to represent the upper range of a continuous distribution rather than a discrete clinical entity. In interpreting the results of the investigations about to be reviewed, it must be kept in mind that the criteria for hyperglycemia tend to vary from study to study.

This review deals with the relation between hyperglycemia and myocardial infarction as observed after recovery from the acute attack or, to the extent that such data are available, antedating it. Hyperglycemia is not infrequently seen immediately after or within the first few weeks after myocardial infarction; three reports may be cited among several others.\(^7\)\(^-\)\(^9\) In such instances, the glucose tolerance may or may not revert to normal, and there is no doubt that at least some of these patients are latent or even overt diabetics. For the present purpose, however, the case will be strengthened if attention is confined to persons whose glucose tolerance remains impaired following recovery.

**Vascular Disease in Diabetes**

The literature is replete with reports on the excessive frequency of coronary and peripheral vascular disease in diabetics; pertinent references are given in several reports.\(^2\)\(^,\)\(^10\)\(^-\)\(^15\) While the existence of this association is not in doubt, its degree is open to question because properly matched control groups are difficult to obtain in clinical studies. Epidemiological data from the town of Tecumseh, Michigan, suggest that the prevalence of different manifestations of arterial disease is about twice as high among diabetic as among nondiabetic men and women in this total population.\(^14\) In a large, industrial population, the incidence of myocardial infarction among men aged 25 to 64 years was 2.55 times higher in diabetics than in controls.\(^16\)

It is frequently stated that coronary heart disease occurs particularly often in young diabetics. If diabetes enhances atherosclerosis, this would be expected. Supporting data are not easily gathered because of the competing and confounding risks of renal disease, duration of diabetes, treatment, and again the need for comparable rates among control subjects. Unpublished data (personal communication from H. H. Marks) based on a comparison of the mortality experience at the Joslin Clinic with the general mortality among white persons in New England indicate that mortality from heart disease at ages 15 to 44 is 4.6 times higher among diabetic males and 6.4 times higher among diabetic females than among the white persons in New England; the corresponding ratios at ages 45 to 74 years are 2.0 and 3.2, respectively.

**Experimental Atherosclerosis and Diabetes**

Considering how much experimental work has been done over the years on both diabetes and atherosclerosis, it is surprising that relatively little is known about the production of arterial lesions in diabetic animals. In 1945, Kendall and associates\(^17\) reported that alloxan causes hyperlipemia in rabbits. Four years later, Duff and McMillan\(^18\) found unexpectedly that feeding cholesterol to alloxan-diabetic rabbits caused less atherosclerosis than was found in control animals, possibly due to the protective effect of a high phospholipid-cholesterol ratio. In rats on high fat diets, alloxan diabetes has no effect on arterial lesions.\(^19\) In cholesterol-fed cockerels, insulin prevented the regression of coronary atherosclerosis.\(^20\) A possibly adverse effect of insulin is also suggested from recent experiments by Mahler\(^21\) indicating that lipase activity in aortas of alloxan-diabetic rats was suppressed by insulin. Serum from persons on high carbohydrate diets leads to less lipid deposition in aortic tissue culture cells than serum from subjects on high fat diets does\(^22\),\(^23\), the relationship, if any, between this and Mahler's observation is not clear. A unifying concept behind all these somewhat confusing data is needed. Further experimental work on the relationship between diabetes and atherosclerosis should be rewarding.

**Hyperglycemia in Vascular Disease**

Against this general background, the question arises how often do persons with coronary disease...
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Heart disease show evidence of reduced glucose tolerance, that is, hyperglycemia. In other words, to what extent is hyperglycemia a risk factor in coronary heart disease, in the same sense as elevated serum cholesterol, high blood pressure, smoking, and other conditions are? A brief review of the evidence will be given.

Using the intravenous glucose tolerance test, Wahlberg, in Sweden, studied 190 survivors from a first myocardial infarction. The prevalence of frank diabetes rose from 12% in those below the age of 50, to 29% between 50 and 69, to 46% at age 70 years and beyond. In addition, an approximately equal number of survivors had borderline results of tests. While glucose tolerance diminishes with age, these values are well above expectation. Brown and associates, on the other hand, did not find lower rate constants for glucose utilization (k-values) in patients as compared with controls in a series of 183 men; according to a personal communication this series has now been extended to 391 men, with similar results; however, these workers used a smaller glucose load than Wahlberg did. Nikkila and co-workers, in Finland, using less glucose than Wahlberg but more than Brown and colleagues, found abnormal k-values, by their definition below 1.2, in 19% of their 41 nonobese patients. There is, obviously, a problem in interpretation on account of differing methods and types of patients, but the evidence favors an association between an abnormal test and coronary disease. The intravenous tolbutamide and glucose tolerance responses of patients with ischemic cardiovascular disease are significantly but weakly associated. The association between abnormal intravenous glucose tolerance and ischemic cardiovascular disease appears to be independent of serum lipid alterations.

Data based on oral glucose tolerance tests are more extensive. A partial summary is given by Wahlberg on 12 studies; the corresponding references may be obtained from his paper. Altogether, 61% of the 590 patients included in these reports had abnormal responses, but the data are not strictly comparable because of differences in patient selection and definitions of abnormality. Still, the general trend is clear. A number of the authors quoted rightly stressed that a large proportion of these patients had latent rather than clinical diabetes. Yet, in Waddell and Field’s series, no less than 78% of their subjects had probable diabetes according to the criteria of Fajans and Conn. While only 41% of the patients in the study by Reaven and colleagues had abnormal tests, this proportion rose to 75% when abnormal responses to either the glucose or the cortisone-glucose tolerance test were taken into account; by contrast, only 33% of the controls showed these abnormalities. Cohen and Shafrir found in addition that during the tolerance test free fatty acids showed an excessive and prolonged decrease which could be interpreted to reflect increased lipogenesis in adipose tissue. If adipose and arterial tissues respond similarly, as proposed by Mahler, cited earlier, a link between these responses and atherosclerosis would suggest itself.

Gorlin and his group have recently drawn attention to the frequency of latent diabetes in patients with coronary heart disease as demonstrated by cinearteriography. In young men with coronary disease, Hatch and co-workers have likewise found a strikingly high prevalence of hyperglycemia. Sollon and Schwartz, reported similarly that there is much resemblance in glucose tolerance between diabetics and patients with coronary disease; they also pointed out that the free fatty acid response to a glucose load in these patients may either be of the type reported by Cohen and Shafrir quoted earlier, or show the delayed decrease seen in diabetics. The different patterns of free fatty acid and also insulin-like activity responses during glucose loading in normal persons and in diabetics of varying stages of severity were described in detail by Shafrir and Gutman. Unduly frequent hyperglycemia in survivors of heart attacks has been reported by others also, namely, Sievers in the large series in Malmö, Aleksandrow and associates from

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Warsaw, and Büchele from Zürich. Indians in East Africa show a high prevalence of both diabetes and vascular disease. The international scope of these findings is noteworthy. By contrast, there is a suggestion that in parts of the world diabetes does not tend to enhance atherosclerosis, for example, among Yemenite Jews in Israel and possibly among the Japanese.

Finally, supporting evidence is now available from epidemiological surveys. The Tecumseh Community Health Study has shown that the prevalence of coronary and other manifestations of vascular disease is higher in the presence than in the absence of hyperglycemia; these associations are independent of serum cholesterol and blood pressure levels. Keen and co-workers have presented similar findings from the Bedford Survey in Britain. These epidemiological data are based on prevalence and are, therefore, biased in that persons who die of coronary disease prior to the survey are excluded. Furthermore, the theoretical if unlikely possibility exists that hyperglycemia does not precede the onset of overt coronary disease but develops subsequently. Incidence data from the Tecumseh study so far are based only on a 4-year follow-up period but suggest that the risk of dying from coronary disease is markedly greater among persons with antecedent hyperglycemia. The only other available data on incidence, as opposed to prevalence, are unpublished observations from the Framingham study. "Casual" blood sugar determinations were made initially whenever the participants happened to come in for examination. Even by this relatively crude measurement, the total incidence of coronary disease and the incidence of deaths from heart attacks during the subsequent 12 years were clearly related to the level of blood sugar.

All these data, taken together, leave little doubt that carbohydrate tolerance is often impaired in coronary heart disease. Almost all investigators who have looked for this association appear to have found it with almost monotonous consistency. In order to state with greater assurance that such impairment actually precedes the onset of clinical disease, further evidence from prospective epidemiological studies is required.

**Hyperglycemia, Hyperinsulinism, and Atherosclerosis**

As part and parcel of epidemiological studies, there is a need for clinical and laboratory data to elucidate the biological mechanisms which link hyperglycemia to events at the cellular level. The demonstration of a plausible mechanism would strongly suggest that the observed associations do indicate, in fact, a cause-and-effect relationship between hyperglycemia and coronary disease. It would be attractive to think that early, preclinical diabetes is associated with an initially delayed but unduly prolonged insulin response and that this hyperinsulinism causes lipid accumulation in the arterial wall, as it does in adipose tissue. The possibility of a detrimental effect of insulin excess on the arterial wall was already raised in the earlier section on experimental atherosclerosis and diabetes. Even though mild diabetics release less insulin per unit of secretory stimulus of glucose, their absolute output of insulin, on account of the more intense hyperglycemia, is greater. Likewise, insulin output in response to a glucose load increases with age and is greater among obese than among other individuals. All these findings suggest that persons prone to coronary disease may often show hyperinsulinism under daily conditions of living.

Turning to survivors from myocardial infarction, Nikkila and co-workers and Peters and Hales did, in fact, commonly find abnormally high insulin responses in their patients. Similar results were obtained by Welborn and associates among patients with hypertension or peripheral vascular disease. Tzagournis and co-workers and Lazarus (personal communication from L. Lazarus) in Australia, have likewise found elevated insulin levels in patients with coronary disease. Vallance-Owen and Ashton believe that the observed phenomena are due to the
presence of excessive levels of synalbumin-insulin antagonist. By contrast, insulin-like activity among patients and matched controls in the Tecumseh study was the same in these two groups. The need is great for further studies of these interrelationships. To avoid divergent and confusing results due to patient selection, the characteristics of both patients and controls in regard to age, sex, overweight, degree of hyperglycemia, and type of hyperlipidemia should be clearly defined. Such careful stratification implies the need for considerable numbers of subjects.

**Associations Between Hyperglycemia and Other Variables**

Taking, then, the association between hyperglycemia and coronary heart disease for granted, the question must be asked whether glucose tolerance is just another way of measuring other risk factors which are better known and more extensively studied. As mentioned earlier, in the experience of the Tecumseh study elevated blood sugar levels showed an association with coronary disease which was independent of serum cholesterol and blood pressure elevation, even though hypertension and hyperglycemia were correlated. On the basis of clinical observations, the frequent coexistence of diabetes and hypertension has, of course, been recognized for a long time. Actually, in his recent Joslin lecture, Conn has used data from the Tecumseh study to buttress his belief that the excessive frequency of hyperglycemia in hypertensives might be explained by the proportion of hypertensive patients whose blood pressure elevation is thought to be due to primary aldosteronism. While this view requires further evidence, it serves to emphasize that hyperglycemia need not necessarily be related only to abnormalities in the intermediary metabolism of fats and carbohydrates but could be due primarily to other influences, for example, electrolyte disturbances such as potassium loss affecting insulin secretion from the pancreas.

Apart from blood pressure and serum cholesterol, there are other coronary heart disease risk factors which could be highly correlated with hyperglycemia. In the data from Tecumseh, the correlations between hyperglycemia on the one hand, and relative weight, skinfolds, serum uric acid, smoking, and physical activity on the other are of a low order of magnitude. It is unlikely, therefore, that any of these variables could account for the findings linking hyperglycemia and coronary heart disease. Unpublished data (personal communication from J. Stamler) likewise show a distinct but quite low degree of association between blood glucose response 1 hour after a 50-g load and other risk factors.

The question concerning the correlation between serum triglycerides and glucose tolerance remains. Dunn and Moses gave 100 g of glucose to nearly 300 men in the fasting state and drew a blood sample 2 hours later. Based on determinations from this sample, there was a slightly negative but nonsignificant correlation between triglyceride and the 2-hour blood sugar level. Albrink and Man a number of years ago showed that glucose may abolish alimentary hyperlipemia, but it is uncertain whether glucose given fasting, as in Dunn and Moses' study, would depress triglycerides. Albrink and Davidson, as part of an extensive study of glucose tolerance and hypertriglyceridemia, reported that fasting glucose and triglyceride levels are not significantly correlated although an earlier study by Albrink and Meigs did show a statistically significant association between these two variables. The current studies by Albrink and Davidson suggest that there is, indeed, a correlation between glucose tolerance and triglyceride levels; in hypertriglyceridemia, glucose clearance and the decrease of free fatty acid in serum are delayed. Harlan and co-workers also noted a significant association between fasting serum triglycerides and blood glucose, determined 2 hours after an overnight fast; moreover, a relation between gain in weight and triglycerides, regardless of blood sugar level, was demonstrated. Carlson and Wahlberg on the other hand, found no relationship between triglycerides and intravenous glucose tolerance.
Ostrander and his colleagues\textsuperscript{57} have recently obtained information on the relationship between fasting triglycerides and the standard glucose tolerance test. Among all the persons with coronary heart disease in the Tecumseh community, those with definite hyperglycemia and with definitely normal glucose tolerance were selected. In the hyperglycemia group, about 1.5 times more persons than expected showed triglyceride elevation. These data are based on relatively small numbers and do not reflect the association between triglycerides and impairment of glucose tolerance in the total population because of the method of selecting patients and controls. Nevertheless, they indicate a correlation between these two variables. It was of considerable interest to find that this correlation was entirely due to a clustering of hyperglycemia and hypertriglyceridemia among the persons with coronary heart disease since there was no association between these variables among the control subjects.

Lastly, the relationship between hyperglycemia and coronary heart disease\textsuperscript{70, 71} must be mentioned, at least briefly. Data from prospective studies in which both serum cholesterol and triglyceride have been measured are still scarce. Therefore, no definite answer can be given to the question which of these two variables may be more predictive. In fact, the question is in itself unfortunate since, according to data from both the Framingham\textsuperscript{72} and Albany\textsuperscript{73} studies, both variables have predictive value. If one believes, as one must, that the metabolic errors causing elevated cholesterol and triglyceride levels are different, despite some overlap, serum cholesterol can be presumed to be a better predictor in some persons and triglyceride in others.\textsuperscript{74}

Summarizing all the data on association between impaired glucose tolerance and triglycerides, it may be stated, in answer to the original question whether these two measurements are really, as it were, two sides of the same coin, that this is probably true in part. The actual strength of this association remains to be determined in an adequately large and representative sample of the general population, taking the possible confounding effect of obesity into account.

These matters are closely linked with the problem of carbohydrate-induced hyperglyceridemia\textsuperscript{75}; none of the patients with this disorder showed an abnormal glucose tolerance test during the control period although the response to tolbutamide was decreased.\textsuperscript{76} More recently, Kuo and Bassett\textsuperscript{77} reported similar findings. It is likely that carbohydrate-induced hyperglyceridemia in its more extreme form represents merely the upper end of a distribution and that the lesser forms of the syndrome may be very common. Nestel\textsuperscript{78} found carbohydrate-induced hyperglyceridemia in a number of patients with coronary heart disease.

If hyperglycemia and hyperglyceridemia, like hypercholesterolemia, predispose to coronary heart disease, it would be of extreme importance to determine the frequency of these various metabolic patterns in the general population. The multiple genes involved are likely to be very common, the accumulation having been caused over the centuries by natural selection.\textsuperscript{79, 80} The expression of this genetic predisposition, however, must largely depend on precipitating factors in the environment. A definitive study of these interrelationships and their influence on the development of coronary heart disease would have to include simultaneous measurements of triglyceride, cholesterol, and glucose tolerance and also to provide knowledge of the usual diet, since Lees and Fredrickson\textsuperscript{81} have shown that some degree of hypertriglyceridemia can be induced in so-called normal individuals. The possible effect of obesity and physical activity must also be taken into account. Lipoprotein typing according to the method of Fredrickson and associates\textsuperscript{82} and insulin responses both by immuno-assay and the fat-pad technique should also be included. Such a study would be ambitious but needs to be done in order to obtain the required answers.

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Diet and Glucose Tolerance

In this review of carbohydrate metabolism and atherosclerosis, the relative role of various dietary carbohydrates and lipids on glucose tolerance must be mentioned briefly. The view is frequently expressed, it would almost appear intuitively, that high carbohydrate intake leads to impaired glucose tolerance. However, the extensive studies by Himsworth\(^5\) suggest that high fat rather than high carbohydrate intake depresses glucose tolerance; he also thought that the decline in the frequency of diabetes during the second world war in Britain was due to a reduction in fat consumption.\(^6\) It does not necessarily follow that a habitual high fat intake will result in diminished glucose tolerance.

A fair amount of work has been done on the effect of various simple and complex carbohydrates on serum lipids but, it would seem, glucose tolerance was not usually measured or reported in these investigations. Mirsky and colleagues\(^7\) found in 1941 that carbohydrate does not induce acetonuria in diabetic patients taken off insulin and that it may actually improve carbohydrate retention. After a long interval, in 1966, Cohen and associates\(^8\) showed in 15 normal human volunteers on a diet in which 20% of the calories came from fat, predominantly saturated, that the oral glucose tolerance was better when the carbohydrate was mainly in the form of bread rather than sucrose. Further studies of this kind are needed, especially on diets with a higher and more usual fat content. Farquhar and co-workers\(^9\) found in 15 subjects, most of whom had greater or lesser degrees of carbohydrate-induced hypertriglyceridemia, that the glucose area after an oral glucose tolerance test was slightly greater on a high carbohydrate than on a high fat diet. If impaired glucose tolerance is causally related to atherosclerosis, what kind of diet will reduce hyperglycemia? The answer, in terms of type and amount of fat and type and amount of carbohydrate, is not clear from these various observations and experiments.

In rats, blood glucose 3 hours after a glucose load was higher during use of a high fat than of a high sucrose diet although a tendency toward the reverse was observed at 1 hour.\(^5\) Also in rats, glucose tolerance was better and insulin-like activity was higher during use of a starch than of a sucrose diet.\(^1\) In rabbits, hepatic lipid is higher during use of a sucrose than of a starch diet.\(^5\) There seems to be a need for an investigation in which various kinds of fat and simple and complex carbohydrates are tested in one and the same experiment, preferably in man.

In contrast to glucose tolerance, a good deal is known about the effect of simple and complex carbohydrates on serum lipids. It might be hoped that carbohydrate food patterns which reduce serum lipids\(^9\) will also have a favorable effect on carbohydrate tolerance. Although current evidence is not clear-cut, it would, perhaps, be a fair summary to say that sucrose increases both serum cholesterol and triglycerides but that this effect is most marked with diets that are relatively low in fat.\(^1\) The matter can be further complicated by taking into account meal frequency since there is a suggestion, supported by observations on so-called adaptive hyperlipogenesis,\(^1\) that lipid levels are lower and glucose tolerance higher in persons who eat more often in the course of the day.\(^1\) Dietary Carbohydrate and Coronary Heart Disease

Lastly, consideration must be given to the view that coronary heart disease may be more closely linked with a high sucrose than a high fat intake.\(^4\) The claim that survivors from myocardial infarction report a higher sucrose intake than controls\(^8\) has not been confirmed by others\(^9\) and is currently being further tested. On the basis of food intake data and death rates in Britain and other countries, Yudkin\(^4\) stated that the trends in arteriosclerotic heart disease mortality are as well or better explained in terms of increased sucrose than of increased fat consumption. Antar and co-workers\(^1\) have...
gone even further and relate the rising frequency of coronary heart disease in the United States largely to the consumption of simple carbohydrates rather than fats since the per capita consumption of the former but not of the latter has increased over the past 50 years. This interpretation has been challenged because there appears to have been a disproportionate increase in saturated fats. There is no justification for being dogmatic about these matters at this time. It is likely that the major geographic differences in the frequency of coronary heart disease are determined in part by differences in the consumption of saturated fats but that a high intake of sucrose, coupled with a high intake of saturated fats, excess of calories, and lack of exercise have an added detrimental effect. This hypothesis has obvious bearing on the prevention of atherosclerosis.

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References


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