

Chapter 18

**Vascular complications in fibrocalculous
pancreatic diabetes**

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Summary

Fibrocalculous pancreatic diabetes (FCPD) is distinctive because of its predilection towards younger subjects, occurrence in the tropics, rapid progression of exocrine damage and predisposition to malignancy. Do the endocrine-related i.e. diabetes-linked complications too occur and progress rapidly as well? This article will focus on the link between FCPD and diabetes-related vascular complications. Increasingly, evidence seems to suggest that microvascular complications, which are specific to the diabetic milieu, are as common in FCPD as compared to other subtypes of diabetes. Macrovascular complications are reportedly rare in these subjects, as they are younger, leaner, and have lower cholesterol levels. However, macrovascular complications are being increasingly reported in FCPD subjects from India. In this article, we focus on the link between FCPD and vascular complications, and also present the data from our center.

Introduction

Earlier, the genesis of fibrocalculous pancreatic diabetes (FCPD) had been attributed to malnutrition.¹ Today, it is increasingly being recognized that FCPD is a form of secondary diabetes.² This paradigm shift has occurred because of the recognition that the etiological links between malnutrition and diabetes are at best tenuous, i.e. pancreatic damage is the reason for malnutrition, and not vice versa. This has led the American Diabetes Association to characterize FCPD as a secondary form of diabetes.³

Accepting this view, it becomes logical to assume that the hyperglycemic milieu in fibrocalculous pancreatic diabetes is essentially dependent on the extent and duration of pancreatic beta cell damage.⁴ A corollary of this view would be that diabetes-related vascular complications would occur as commonly in FCPD as in type 1 or type 2 diabetes, as it has been well proven that diabetic-vascular complications are inextricably linked to the duration and severity of hyperglycemia.^{5,6} Presently, the bulk of available evidence on FCPD supports this view, however there are some caveats.

Microvascular disease

The microvascular complications, i.e. neuropathy, nephropathy and retinopathy are relatively diabetes-specific. Unlike *macrovascular* complications like coronary artery disease, which can also occur in non-diabetics, the unique pattern of microvascular damage is not seen in non-diabetic individuals. Studies on fibrocalculous pancreatic diabetes have shown that *microvascular* complications do occur in them as commonly as in other subtypes of diabetes.⁷

As early as in 1985, it was reported that sight-threatening retinopathy could occur in FCPD.⁸ In this study of 40 patients from South India with FCPD, it was reported that 13 subjects had retinopathy. In addition to background retinopathy, the authors reported the occurrence of macular edema and proliferative retinopathy requiring laser therapy. Thus in this study, diabetic retinopathy was present in about one third of subjects with FCPD. Subsequently, retinopathy has been reported to be about 30% in FCPD.⁹

The prevalence of overt nephropathy among FCPD subjects is about 10%.⁹ However, microalbuminuria could be more common; in a study on African subjects with pancreatic diabetes about 33% had microalbuminuria.¹⁰ Notably, in the only published study on the long-term survival of subjects with FCPD, diabetic nephropathy was the leading cause of death.¹¹

As far as neuropathy is concerned, the prevalence is reported to be about 44%, making it a common microvascular complication of diabetes.¹² Most subjects with fibrocalculous pancreatic diabetes also have malabsorption due to pancreatic enzyme deficiencies. Therefore, it is possible that nutritional deficiencies, and even the additive effects of moderate alcohol consumption might increase the occurrence of neuropathy. In contrast to other diabetic complications, neuropathy seems to correlate very well with the duration of diabetes, and in one study, autonomic neuropathy was found in over 60% of subjects with FCPD after 16 years of diabetes.¹³

Overall, these data seems to suggest that microvascular diseases are as common in FCPD as in other subtypes of diabetes.¹⁴ It is important to

address the issue of whether vascular complications are as common in FCPD as compared to other subtypes of diabetes. In a recent study, FCPD was compared to other subtypes of diabetes in the young.¹² As compared to age-matched subjects with type 2 diabetes, malnutrition modulated diabetes, and type 1 diabetes, subjects with FCPD had a similar prevalence of microvascular disease. It was reported that the prevalence of neuropathy was higher in subjects with fibrocalculous pancreatic diabetes as compared to other subtypes of diabetes. This study showed the prevalence of microvascular complications relatively early on after diagnosis. At our center too, microvascular complications are seen in about one-fourth of subjects with FCPD (see below). Taken together, these studies confirm the need to screen for microvascular complications in these subjects.

Macrovascular disease

The issue of macrovascular disease in fibrocalculous pancreatic diabetes is quite fascinating because this gives an insight into the changing profile of FCPD. To begin with, macrovascular complications of diabetes are rare in FCPD. This has been attributed to three factors: the younger age of the subjects, lower body mass index and lower cholesterol levels.¹⁴ However, reports of macrovascular complications have become more frequent.¹⁵ Stroke, peripheral vessel disease (PVD), coronary artery disease (CAD), and hypertension have all been reported in FCPD.¹⁶⁻¹⁸ It has been reported that about 4.7% of subjects with FCPD have peripheral vessel disease, and about 5% have coronary artery disease.⁹

While the association between FCPD and macrovascular disease is now only in the realm of anecdotal case reports, there are several interesting facets to this issue. It is tempting to speculate that this changing profile is in some way linked to the increasing occurrence of insulin resistance syndrome (including type 2 diabetes and coronary artery disease) in the Indian subcontinent. In other words, could the predisposition to macrovascular disease be linked to the co-existence of type 2 diabetes in these subjects? This is an interesting area for further study, but it is difficult to design a trial to address this issue, obviously because of the difficulty in conclusively proving the co-existence of type 2 diabetes and FCPD in these subjects.

Could the macrovascular disease be in some way linked to insulin resistance? Using parameters of insulin resistance, a recent study has investigated insulin sensitivity in FCPD and compared the same with other age-matched subtypes of diabetes.¹² Four groups of young diabetic subjects were studied: FCPD, type 2 diabetes, malnutrition modulated diabetes, and type 1 diabetes. The area under insulin curve (AUC) was measured by doing a glucose tolerance test, and checking serum insulin levels every 30 minutes for two hours. In this study, FCPD subjects had higher insulin levels as compared to subjects with type 1 diabetes as well as those with malnutrition modulated diabetes mellitus.¹² Among young diabetics, only type 2 diabetics had higher AUC values. In addition, in a second analysis of the same group, FCPD subjects had higher values of insulin resistance as measured by the homeostasis assessment model.¹⁸

The intravenous insulin infusion test showed that over 60% of these FCPD subjects were insulin resistant.¹² The study concluded that subjects with FCPD had significant values of insulin resistance when compared with type 1 diabetes as well as malnutrition-modulated diabetes. As the extent of hyperglycemia was similar in these groups, the defect in insulin action cannot be attributed to glucose toxicity, i.e. a toxic effect of hyperglycemia on the insulin action pathways. However, this observation is somewhat intriguing and could well be a chance finding, considering that other reports have shown that the amount of insulin required in FCPD is only about 40 units per day.^{14,18}

Interestingly, it has also been reported that young subjects with FCPD had a significantly higher triglyceride levels (when compared with age-matched type 1 diabetics, malnutrition-modulated diabetes as well as controls).¹² Hypertriglyceridemia is associated with both pancreatic damage and insulin resistance. It would also be useful studying the effects of oxidant stress in FCPD, as oxidant stress has been linked to the genesis of FCPD as well as with the insulin resistance syndrome.¹⁸⁻²¹

Vascular complications in FCPD: our experience

The audit from the pancreas clinic at the Amrita Institute of Medical Sciences also shows a similar profile when compared with other studies

regarding the prevalence of microvascular and macrovascular complications. A total of 48 cases of fibrocalculous pancreatic diabetes, seen over a period of one year, underwent evaluation for diabetic complications, glycemic control and lipid profiles.

The mean age at onset of FCPD was 33.4 yrs. The mean duration of diabetes at presentation was 8.8 years. Even though the majority of subjects (28/48) had onset of DM after pancreatitis, a significant number (13/48) had DM preceding CCP. Most of the patients were either non-obese or lean and the mean BMI was 18.8 kg/m².

Glycemic control as assessed by the mean HbA1c was fair (8.2 %), but the mean fasting and postprandial plasma glucose levels were high (159mg/dl and 306mg/dl respectively) at the time of initial visit. We postulate that these uncontrolled blood glucose values (given the concomitant HbA1c value) could be related to repeated episodes of hypoglycemia and hyperglycemia, thus leading to brittle diabetes in the FCPD patients. The lipid profiles also showed a favorable trend with a mean triglyceride value of 106 mg/dl, a mean LDL of 112.9mg /dl and a mean HDL of 48 mg/dl. In general, subjects with FCPD are reported to have low cholesterol levels; the relatively high LDL levels in our series are probably linked to suboptimal glucose control.

About one fourth (23%; 11/48) of our subjects had microalbuminuria, diagnosed when the value for urine albumin-creatinine ratio was more than 30 ug/mg. A similar proportion i.e. 27%(13/48) had neuropathy as diagnosed by neuropathic symptoms along with abnormal biothesiometry.

Among the FCPD subjects, 15 %(7/48) had retinopathy on dilated fundus examination. Coronary artery disease as evidenced by history of angina or myocardial infarction and/or ECG changes was present in only 4.2%(2/48) and peripheral occlusive vascular disease detected by ankle brachial index and confirmed by doppler evaluation was seen in only 2.1%(1/48)cases. To summarize, our experience is in keeping with that from other centers in the country, with about one fourth of subjects having microvascular complications. The prevalence of macrovascular disease was low in our series.

Conclusions

Microvascular complications are as common in FCPD as compared with other subtypes of diabetes. Macrovascular disease, particularly coronary artery disease is rare. However, there are several reports of macrovascular complications in FCPD, and the reasons for them are an interesting area for future research.

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