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# IMPAIRED GLUCOSE TOLERANCE—DOES IT CAUSE NEUROPATHY?

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The publication of the Diabetes Control and Complications Trial (DCCT) laid to rest much of the controversy surrounding the role of hyperglycemia in diabetic neuropathy.[11,12] This study showed that intensive insulin therapy, coupled with improved glycemic control, reduces the severity of diabetic complications and, more importantly, decreases the risk of developing these complications. This was the first large prospective study to show that careful regulation of blood glucose can prevent development of neuropathy in diabetic patients. Despite the evidence that hyperglycemia is coupled with neuropathy, it has been assumed that neuropathy results only from significant hyperglycemia and is not related to impaired glucose tolerance (IGT). In the presence of mild and episodic hyperglycemia, alternative causes for neuropathy are sought.

## WHAT IS IMPAIRED GLUCOSE TOLERANCE?

Despite attempts to improve and standardize categories of impaired glucose regulation, controversy still surrounds the definition of IGT. In a 1997 consensus statement, the American Diabetes Association (ADA) revised its recommendations for diabetes screening for the first time since 1973.[8] It endorsed fasting venous plasma glucose (FPG) as the primary test for hyperglycemia, rather than relying on the oral glucose tolerance test (OGTT). A new, lower FPG of 126 mg/dl, on two or more tests on different days, was recommended for the diagnosis of diabetes in both clinical and epidemiological settings. In 1998, the World Health Organization (WHO)[8] endorsed most of the ADA criteria but retained the OGTT. Based on the OGTT, a 2-h glucose of 200 mg/dl is diagnostic of diabetes, whereas >140 mg/dl but <200 mg/dl with a FPG < 126 mg/dl signifies IGT. An intermediate designation, of impaired fasting glucose (IFG), was introduced by the ADA and defined as a FPG > 110 but <126 mg/dl.[8] The ADA initially considered IFG to be analogous to IGT, although the WHO report made it a separate category. Although both IFG and OGTT correlate with insulin resistance, corresponding to a level of hyperglycemia above which acute-phase insulin secretion is lost in response to a glucose load, several studies have shown that IFG underestimates the prevalence of impaired glucose regulation in population studies. Furthermore, use of the ADA-defined IFG, rather than IGT with an OGTT, underestimated the hyperglycemic risk for cardiovascular disease. Thus, the FPG is probably too insensitive to accurately determine IGT and an OGTT should therefore be performed in patients with undiagnosed neuropathy.

## CARDIOVASCULAR DISEASE AND IMPAIRED GLUCOSE TOLERANCE

Several prospective studies have examined the risk of cardiovascular disease in subjects with IGT and have shown an increased risk for coronary and carotid atherosclerosis.[1,6] The Diabetes Prevention Program in the United States has randomized 3234 participants with IGT into a three-arm study testing the efficacy of intensive lifestyle management and pharmacological therapy in preventing progression to diabetes.[13] In addition, subjects in this study will be followed for an average of 4.5 years to determine whether there is a decrease in the risk for cardiovascular disease. The range of 2-h post-OGTT plasma glucose in this study is approximately 142–198 mg/dl and will provide representative information on IGT subjects based on the age, sex, and racial distribution in the United States population. The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP NIDDM) in Canada and Europe has randomized over 1000 patients with IGT into a 3-year study

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to prevent disease progression. The results of endpoint measures from these studies have not been published at this time but will provide important prospective information about the risk of progression to diabetes and of developing cardiovascular disease in subjects with IGT. Unfortunately, these studies will not provide information about the prospective risk of neuropathy in IGT subjects.

## NEUROPATHY SEVERITY IS ASSOCIATED WITH HYPERGLYCEMIA

The DCCT established a clear link between impaired glycemic control, neuropathy, and retinopathy. The study prospectively followed 1441 insulin-dependent type I diabetics for a mean of 6.5 years to assess the effect of intensive insulin therapy on the development of diabetes complications.[11,12] Patients were divided into primary-prevention and a secondary-intervention groups and treated with intensive or conventional insulin therapy. In the secondary-intervention cohort, intensive insulin therapy reduced the appearance of clinical neuropathy by 60% over a 5-year follow-up. The results for patients who had neither retinopathy nor significant albuminuria at the start of the study (primary-prevention cohort) were even more impressive. In this group, intensive therapy reduced the appearance of neuropathy by 69% compared with only 10% with conventional therapy, indicating that early optimal glycemic control can prevent the development of neuropathy prior to developing retinopathy and microvascular injury.[11,12] Furthermore, it is clear from the data that any increase in glucose above normal is associated with an increased risk of end-organ injury, including neuropathy. The results of the DCCT and other similar studies suggest that early impaired glycemic control is associated with peripheral neuropathy and may be the primary pathology at presentation prior to developing other end-organ injury, such as retinopathy or nephropathy.[2,11] Although diabetics may have neuropathy at presentation, intervention in subjects with IGT may prevent some, if not all, cases of neuropathy.

## UNDIAGNOSED SENSORIMOTOR NEUROPATHY

Despite careful evaluation, the cause of a sensory or sensorimotor neuropathy may remain unknown. Intensive investigation of neuropathy improves the diagnostic yield to 80%.[4] However, this still leaves approximately 20% of patients in whom the etiology of the neuropathy is undetermined. Neuropathy occurring early in diabetes is usually characterized by sensory symptoms, including pain and autonomic dysfunction. In a survey of 669 patients with early diabetic neuropathy, sensory symptoms were present in more than 60%, impotence in nearly 40%, other autonomic involvement in 33%, but evidence of motor involvement in only 12%.[14] These clinical findings suggest prominent early involvement of the small unmyelinated nerve fibers that mediate pain, temperature sensation, and autonomic function. Additional evidence that small fibers are involved comes from quantitative sensory studies in diabetics. Abnormal perception of cold, heat, and pain, mediated by small fibers, and hyperesthesia is observed as an indicator of mild diabetic neuropathy.[3] Furthermore, the positive sensory symptoms of pain and paresthesias may bring patients to medical attention before other signs of diabetic end-organ injury (retinopathy, microproteinuria, cardiovascular complications) are apparent. Thus, there is good evidence that abnormal small-fiber function, as seen in painful diabetic neuropathy, is an early finding in impaired glucose regulation.

Two studies in the current issue of *Muscle & Nerve* suggest that at least some cases of idiopathic neuropathy may be due to undiagnosed IGT. In the study by Singleton, Smith, and Bromberg,[10] patients coded as having idiopathic neuropathy after intensive diagnostic screening underwent testing for IGT. Of the original group, 31% of patients who had glucose measured had diabetes mellitus by ADA criteria. Of the remainder, 17% had impaired glycemic control (IGT or impaired FPG). In comparison, the prevalence of IGT in the general population is approximately 15–20% for subjects of comparable age. When patients with painful sensory polyneuropathy were examined as a subgroup, 35% had IGT. Based on this study, patients with painful sensory neuropathy are more likely to have IGT than a U.S. population group of similar age. Furthermore, the degree of nerve conduction and electromyographic abnormalities paralleled the severity and duration of hyperglycemia, being worse in patients with diabetes mellitus compared with those with IGT.

Novella, Inzucchi, and Goldstein's study of 76 patients with idiopathic polyneuropathy[7] produced a similar conclusion, namely, that patients with painful sensory neuropathy are more likely to have IGT. In the cross-sectional study, all subjects underwent extensive screening to establish other causes of neuropathy and patients were matched to literature controls by age and race. Of 76 patients, 24 had abnormal glucose regulation: 13 (27%) had IGT and 11 (23%) had previously undiagnosed diabetes by ADA criteria. These rates are higher than those reported by Harris et al.[5] The Harris data, however, were obtained in a U.S. population study with sub-

jects ranging in age from 20 to 74 years and cannot readily be compared with subjects obtained from a selected, referral-based cohort. As in the study by Singleton et al.,[10] Novella and colleagues[7] found impaired glucose regulation was more common in patients with painful neuropathy. In subjects with painful sensory symptoms ($n$ = 28), 36% had IGT and 29%, diabetes mellitus.

Both these studies approach the question of whether neuropathy is associated with impaired glucose regulation by defining the subject group as already having neuropathy. The studies retrospectively compare the frequency of IGT with the presence of neuropathy in hospital-based patient groups. Unfortunately, this approach leads to bias in cohort selection and interpretation of data. Thus, one cannot determine whether the prevalence of neuropathy is greater in a patient with IGT. Nevertheless, the high frequency of IGT in albeit small groups of patients with painful sensory neuropathy raises a tantalizing possibility that at least in some patients, IGT may be related to neurologic disease.

## POPULATION-BASED STUDIES OF IGT

The comparison control group used by both studies published in the current issue of *Muscle & Nerve* is from a population-based study performed in the U.S.[5] In the Third National Health and Nutrition Examination Survey (NHANES III) completed in 1994, 2844 subjects aged 40–74 years underwent a 75-g OGTT. In NHANES III, 2.7% of subjects had undiagnosed diabetes and 15.8% had IGT in the 40–74-years subsample. In all subjects aged 60–74 years, 20.7% had IGT. In the studies described in this issue of the Journal, the median age range of subjects was 60–65 years and the percent of subjects with IGT and neuropathy was similar to the population-based study (NHANES III), but the percent of patients within the subgroup of painful sensory neuropathy who also had IGT was substantially higher than in the NHANES III study. However, caution must be used in comparing cross-sectional studies[7,10] with a prospective population-based study.

## TREATMENT OF IGT-RELATED COMPLICATIONS—A SOCIETAL PERSPECTIVE

Between that which we regard as normal glycemia and frank diabetes, there lies a gray area of impaired glucose regulation affecting a large proportion of the population. If patients with IGT are at risk of developing disease, then should rigorous glycemic control be instituted, including drug therapy, and what would be the cost and benefit of such an approach from a societal perspective? Answers to these questions are beset by the need for more population-based evidence that IGT is associated with a similar spectrum of disease as diabetes and the more fundamental question of how to define IGT in order to determine subjects at risk. If every subject with IGT were treated, the implications for management of diabetes would be considerable. Almost 20% of Americans over age 65 have diabetes, and this is likely to exceed 30% by 2010. Treatment of diabetes already accounts for over 100 billion dollars in annual health-care expenditures.[9] The overall prevalence of neuropathy in diabetics is estimated to be between 20 and 60%, and more than half of all patients followed longitudinally will develop clinical symptoms of neuropathy after 25 years of diabetes. Thus, management of neuropathic complications accounts for a considerable proportion of total health-care expenditures. Potentially, a concerted effort to improve diet and reduce obesity might decrease the incidence of impaired glucose regulation in at-risk populations and prevent or reduce the severity of diabetes complications such as neuropathy. This, in turn, will likely translate into a reduction in cost of care and increase in quality of life. Unfortunately, we have only begun to recognize the threat to our society from diabetes and its complications, and it is likely to be a considerable time before the societal benefits of improved prevention are realized.

In conclusion, there is strong evidence supporting an association between IGT and cardiovascular disease and between hyperglycemia and neuropathy. The two papers in the current issue of *Muscle & Nerve* indicate that many patients with undiagnosed neuropathy have IGT. However, large prospective population-based studies, coupled with evidence that primary intervention prevents neuropathy, are needed to confirm an association between IGT and neuropathy. If the two are linked, then the ramifications for physicians and society will be considerable.

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