More than 60% of patients with chronic idiopathic axonal polyneuropathy (CIAP) were found to have undiagnosed abnormal glucose metabolism in a study of 100 patients with the neurologic disorder.

Patients with chronic idiopathic axonal polyneuropathy typically present with slowly progressive symptoms of "burning feet" or other unpleasant sensory foot symptoms in late adulthood. Electrophysiologic testing usually shows evidence of a distal length-dependent axonal process. Underlying causes - toxic exposures or medical conditions such as diabetes, or autoimmune disorders - are identified in only 7% - 30% of patients, according to a study in the Archives of Neurology. Recent research has suggested that in patients with CIAP, the rates of undiagnosed diabetes and impaired fasting glucose are nearly twice those of the general population.

Study investigators Charlene Hoffman-Snyder et al at the Mayo Clinic assessed 100 consecutive patients who were treated for CIAP with no known cause at the Mayo clinic between 2003 and 2005. The 60 women and 40 men underwent extensive diagnostic work-ups including nerve conduction studies and 2-hour fasting glucose tolerance testing.

A total of 62 (62%) had abnormal results on the 2-hour glucose tolerance test: 38 were classified as having IGT and 24 as having diabetes mellitus. This compares with a published rate of 33% in the general, age-matched U.S. population (Arch. Neurol. 2006;63).

Together with the findings of previously published studies, these results suggest that impaired glucose tolerance and impaired fasting glucose are risk factors for CIAP. They also support the idea that peripheral nerve dysfunction predates the development of frank diabetes and may even be the earliest detectable sign of the disease.

The 2-hour glucose tolerance test can be extremely valuable in the work-up for CIAP and other chronic neuropathies of unknown cause, even though it is often avoided by busy health care professionals, perhaps because of the inconveniences posed by the testing procedure.

A new class of drugs for type 2 diabetes shows promise in reducing blood glucose, improving beta-cell function, and helping patients control their weight-all via one oral dose per day, it was reported at the annual scientific sessions of the American Diabetes Association.

Phase III results for the dipeptidyl peptidase (DPP)-4 inhibitors vildagliptin (Novartis) and sitagliptin (Merck & Co.) were presented.

DPP-4 is the enzyme that naturally breaks down the gastrointestinal hormone called glucagon-like peptide (GLP)-1. John B. Buse of the University of North Carolina explained that naturally occurring GLP-1 is released among L cells in the GI tract when food is consumed. Its release promotes the synthesis and release of insulin, lowers levels of glucagon, induces satiety by slowing gastric emptying, and possibly stimulates beta-cell growth and neogenesis.

Inhibition of DPP-4 is intended to help maintain levels of GLP-1.

Both DPP-4 inhibitors will be reviewed for approval and are proposed for use as monotherapy and as adjuncts to metformin as well as pioglitazone.
Ameet Nathwani of Novartis noted that vildagliptin showed high efficacy, "placebo-like" tolerability, ease of use, and potential for long-term disease modification. He presented data of vildagliptin combined with pioglitazone, wherein 65% of patients achieved the HbA1c target of 7% or less, versus 43% of patients on either drug alone. Moreover, there was, with the combination, up to a 2.8% reduction in patients whose HbA1c was higher than 9%. Vildagliptin also resulted in no overall weight gain in the study cohort. Moreover, obese patients on the combination therapy had a decline in their HbA1c of 2.2%.

Nathwani also presented new pooled monotherapy data showing a 1.1% drop in HbA1c, upon initial use of the drug by treatment-naive patients. And his group saw an additional 1.1% drop when the drug was given to patients for whom metformin failed to achieve their target HbA1c.

As to tolerability, a low incidence of hypoglycaemia was noted, even when the drug was used in combination with insulin, as well as superior gastrointestinal tolerability, compared with metformin particularly regarding incidence of diarrhoea.

Once-daily dosing of vildagliptin was not associated with any interactions with drugs commonly used in diabetes, and no dose adjustments anticipated for elderly populations or patients with renal or hepatic impairment.

Nathwani said that the drug's islet-cell effects "suggest potential for long-term disease modification" by suppressing glucagon and enhancing glucose-dependent insulin secretion. The drug was associated with a nearly fivefold increase in beta-cell function, and it improved first-phase insulin response and insulin sensitivity in the study patients.

Peter Stein of Merck & Co. presented preliminary data on a new DPP-4 inhibitor, sitagliptin. In a 12-week monotherapy trial conducted in Japan, sitagliptin was associated with a 1.05% average reduction of HbA1c. In addition, an 18-week multinational trial showed a 0.6% greater reduction than seen with placebo. A 24-week multinational trial of sitagliptin showed a 0.8% reduction, compared with placebo.

Monotherapy trials studied 100-mg and 200-mg doses in more than 1,500 patients to determine if the increased dose showed greater efficacy. Stein reported that even at the 200-mg dose, there were no safety issues, with a tolerability profile similar to that seen with placebo. This was true of hypoglycaemia in general and the incidence of severe episodes. Stein noted a study comparing results with baseline HbA1c showing "substantial improvements." Moreover, in patients with HbA1c of more than 9%, his group saw mean reductions of up to 1.5%.

Trials evaluating the benefit of adding sitagliptin to metformin and to pioglitazone showed progressive HbA1c reduction over the 24-week period. Adding sitagliptin to metformin in patients with mild to moderate hyperglycaemia (mean baseline HbA1c of 8%) resulted in a 0.65% reduction, compared with placebo. When added to pioglitazone, sitagliptin achieved a 0.7% reduction, compared with placebo.

Sitagliptin's effects on beta-cell function showed "substantial improvements," Stein said, bringing reductions in the insulin/proinsulin ratio.

Stein concluded that these data show sitagliptin enhances natural glucose regulation and improves glycaemic control when used as either monotherapy or combination therapy, with a low incidence of hypoglycaemia and a neutral effect on body weight.

Late-breaking data issued by Merck at the sessions reported sitagliptin was as effective as glipizide at lowering glucose levels. In a randomised controlled trial of 793 patients, those on sitagliptin lost a mean of 1.5 kg over 52 weeks, whereas patients on glipizide gained an average of 1.1 kg.

**Tuning Fork Neuropathy Test Found Effective**

Results of a tuning fork test to identify neuropathy appear to be reproducible in a non-diabetic population, according to findings from a blinded, observational study. In a presentation at the annual meeting of the American Association of Clinical Endocrinologists, David Oyer of Northwestern University, Chicago, described how he and an associate used a tuning fork test to evaluate 147 patients aged 40 years and older. All patients had a history of sciatica, cerebrovascular accident, or chemotherapy.

To perform the test, a C128 tuning fork was struck to make the ends clang together, and then patients were shown the difference between the vibration sensation and pressure on the patient's toe, malleolus, knee, or sternum.

The tuning fork test was performed again at the end of the dorsal bony prominence of the patient's big toe proximal to the nail. Blinded, the patients then indicated when they could no longer feel the vibration.

Vibration sensation duration was measured in both feet. Patients repeated the test, and the average number of seconds was taken to represent final scores, which were then analysed for correlation between the right versus left foot, statin versus non-statin use, and overall difference in sensation by
What’s the preferred first-line antihypertensive agent in type 2 diabetic patients with hypertension and macroalbuminuria? It’s an angiotensin II receptor blocker (ARB), according to American Diabetes Association’s treatment guidelines.

For hypertensive type 2 diabetic patients with microalbuminuria – as defined by a 24-hour urinary albumin excretion rate of 30-299 mg – the guidelines list both ACE inhibitors and ARBs as the preferred initial treatment choices, based upon level A data showing that they delay progression to macroalbuminuria (Diabetes Care 2003;26:S33-50).

But ARB’s were singled out as the first-line antihypertensive drug class in patients with macroalbuminuria. The guidelines urge that an ARB “should be strongly considered” in such patients on the basis of compelling level A evidence that this drug class reduces the rate of progression to diabetic nephropathy. That study involved 45 diabetes patients who had vibration test scores of 0-8 seconds, indicating some level of neuropathy. Of those 45 patients, only 16 had abnormal monofilament test results (Endocr. Pract. 2004;10 [Suppl. 1]:20).

"The clanging tuning fork test detects neuropathy at a much earlier stage than the monofilament test," Oyer said. "It can be an accurate gauge of somebody’s neuropathy and either encourage them or make them more motivated to control their blood sugar levels to prevent future problems.

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The supporting data come from several clinical trials, including the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, as well as the Irbesartan Diabetic Nephropathy Trial (IDNT).

But the most impressive evidence of the reno-protective benefits of ARB therapy comes from the Irbesartan Microalbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients (IRMA II) trial.

In IRMA II, 590 microalbuminuric type 2 diabetic patients with hypertension were randomised to 150 or 300 mg/day of Irbesartan or placebo in addition to other antihypertensive agents as needed to achieve good BP control. The 5.2% rate of progression to nephropathy at 2 years in patients on 300 mg/day of Irbesartan represented a 70% reduction in the relative risk of the primary study endpoint, compared with placebo (N.Engl.J.Med. 2001;345:870-8).

Most diabetics who are hypertensive “already have some degree of nephropathy and microalbuminuria, and therefore one should really consider ARBs in all patients who have diabetes and hypertension,” said Schroeder, from Stanford University.

The notion that combined ARB and ACE inhibitor therapy might have additive cardioprotective effects superior to those of either agent alone is being put to the test in the randomised, double-blind Ongoing Telmisartan Alone or in Combination with Ramipril Global Endpoint Trial (ONTARGET). The study involves roughly 25,000 patients with a history of cardiovascular disease, stroke, or diabetes who have been randomised to the ARB, ACE inhibitor, or both. Results are due to be reported next year.
Metformin gave only a modest additional benefit to a 12-week program of nutritional counselling for obese non-diabetic children and their families, Radhika Purushothaman reported at a meeting of the Eastern Society for Paediatric Research.

Given the rising incidence of obesity, insulin resistance, and diabetes among children and adolescents, physicians and clinical researchers are trying just about everything to get a handle on these problems. Metformin and other insulin-sensitising drugs may be helpful, but the high prevalence of gastrointestinal side effects and the fact that these drug therapies are more or less lifelong commitments mean that they should be used very carefully.

A 2002 study of more than 3,200 obese non-diabetic adults with impaired glucose tolerance showed that metformin could improve insulin sensitivity and delay progression to diabetes. "There's no question that insulin sensitisers can delay progression in adults, but so can lifestyle interventions if you get to the patients in the early stages of insulin resistance and impaired glucose tolerance," said Purushothaman of the Infants and Children's Hospital, New York.

The jury is still out on the value of metformin in the paediatric population.

Purushothaman and her colleagues set out to determine if the addition of metformin would improve clinical outcomes of a 12-week diet and lifestyle intervention that involved a cohort of 51 obese but non-diabetic children and early adolescents.

The program comprised weekly sessions that involved parents and caregivers teaching the children the basics of nutrition, healthy diet, and exercise. This was followed by monthly maintenance sessions for another 3 months. Fifteen of the 51 subjects also took metformin 1,000 mg, twice daily during the study period. The investigators did full endocrine, behavioural, and nutritional assessments at baseline, at the close of the 12-week program and at 6 months from baseline.

Neither the lifestyle intervention alone nor the lifestyle program plus metformin had statistically significant impact on body mass index (BMI), although both produced measurable BMI reductions.

Among the 15 patients taking metformin, mean BMI went from 36 to 35; among those in the lifestyle change program alone, BMI went from 30.7 to 29.1. The lifestyle change program did produce significant effects on triglyceride levels, which went from a baseline mean of 147 mg/dl down to 100 mg/dl at the close of the study. Fasting insulin levels also dropped, from a baseline of 20.7 microunits per millilitre down to 14 microunits per millilitre. Somewhat surprisingly, this did not translate into a significant change in fasting blood glucose levels. High-density lipoprotein cholesterol levels were essentially unchanged in the lifestyle intervention alone group.

Among those taking metformin, triglyceride levels also dropped, from a baseline mean of 208 to 144 mg/dl at 6 months. Fasting insulin levels also dropped, from a baseline of 35.3 down to 28.1. However, mean fasting glucose levels actually increased in this group, from a baseline of 84 mg/dl to 91 mg/dl. "This was totally surprising, and we do not know how to explain it," said Purushothaman at the meeting. Metformin did produce a statistically significant increase in HDL cholesterol levels, from 36.8 mg/dl to 40.0 mg/dl.

This study confirms that a carefully planned lifestyle change program that involves the families of obese children and teens can have measurable benefits on overall health, although it may not substantially reduce BMI.

For metformin, the results "were definitely not as clear-cut as we had expected," she said. "Metformin can be considered as an adjunct for obese adolescents, as it has good effects on lipids and insulin, but it did not change the BMI." That said, the drug should be used only when truly necessary. "There was lots of diarrhoea, bloating, and nausea among the kids taking metformin, so the adverse effects are significant."