NEUROMetrix®

Evaluation of Diabetic Peripheral Neuropathy (DPN):

An Overview

Kenneth Snow, MD, MBA

Introduction

Peripheral neuropathy is a common complication of diabetes. Historically, diabetic peripheral neuropathy (DPN) is diagnosed based on history, physical exam and some simple in-office tests. While this testing is easy to perform, it is limited in terms of its accuracy. While nerve conduction studies provide a greater degree of accuracy, the complexity and cost of the testing have precluded their use in a routine evaluation. Advances in technology have now made available the ability to perform in-office nerve conduction testing. NC-stat DPNCheck allows the physician to obtain accurate nerve conduction data to assist in the assessment of DPN. This paper reviews traditional testing methods and their limitations. NC-stat DPNCheck is then reviewed. Finally, the benefits of earlier detection of DPN and the potential for impact on care are discussed.

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Monofilament Testing

History

Originally developed by von Frey in the late 1800s, the first monofilaments used horse hairs of different diameters and lengths to test pressure sensation of the skin. Semmes and Weinstein revived this technique in the late 1950s to study peripheral neuropathy in brain-injured veterans, using a nylon filament embedded in a plastic handle.[1] Leprosy is one of the most common neuropathies in the world and affects sensory as well as motor and autonomic function. The monofilament was first used to assess sensitivity in leprosy patients in Nigeria in the late 1960s.[2]

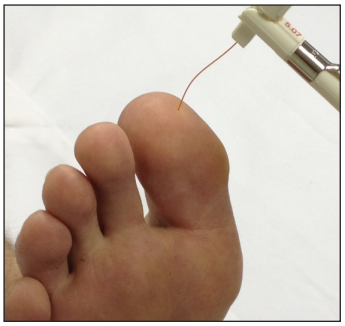
Paul Brand, a leprosy researcher in India, came to the United States in 1965 to head the leprosarium of the US Public Health Service in Carville, LA. While there he noted that people with diabetes had limb injuries and complications similar to those of people with leprosy.[3]

Testing Location

The first publication using the Semmes-Weinstein monofilament in the evaluation of patients with diabetes came from Brand's work at Carville reporting results in patients with Hansen's disease or diabetes.[4] There have been several different recommendations for the testing site and conflicting recommendations have been published on the proper sites for testing. Studies done at Carville involving patients with leprosy or diabetes specified 10 sites distributed over the plantar surface of the toes, metatarsal heads, insole, and heel, and the dorsum of the foot.[4,5] It must be noted that the peripheral neuropathy in leprosy can present in a patchy fashion affecting various parts of the foot first. This is not the case in the diabetic foot since DPN affects more distal areas first, so that it is highly unlikely a patient will develop loss of sensation in the midfoot or hind foot prior to loss in the forefoot and toes. Indeed, in the diabetic foot, the plantar aspect of the forefoot was shown to provide better discrimination between those who did and did not have ulcers compared to the heel.[6]

The International Cooperative Group for Clinical Examination Research studied 304 patients with peripheral neuropathy and found that four plantar sites on the forefoot (great toe and the metatarsal heads of the first, third, and fifth ray) identified 95% of the patients who had one or more absent sensation sites when eight plantar sites were tested.[7] Kumar, in assessing the monofilament as a screening tool in diabetes tested only on the great toe, as shown in Figure 1.[8] Perkins tested the dorsum of the great toe

Figure 1.



just behind the nail bed in assessing the sensitivity and specificity of the monofilament.[9] Testing of the ventral surface of the great toe provided no benefit compared to the dorsum.[10]

Presently, many physicians test at the four plantar locations identified by the International Cooperative Group while others test over the great toe. Some test over other toes or at other sites. The differing approaches can lead to different interpretations and hence less reproducible results.

Testing Number

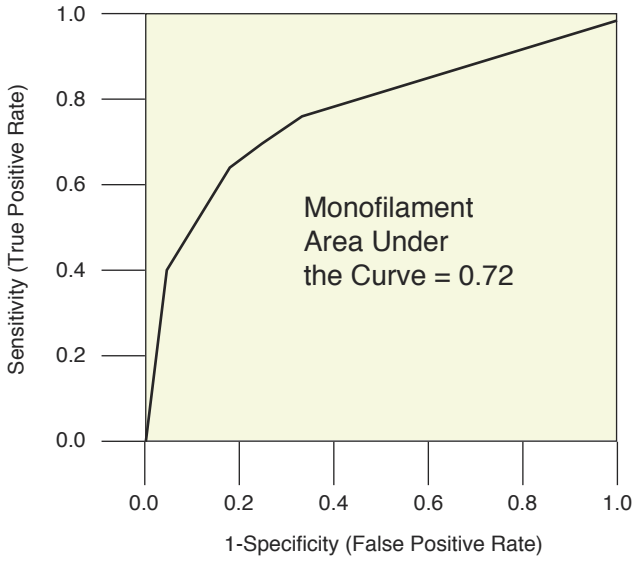
A further issue is the number of times a patient needs to be challenged with a monofilament for an adequate test. Optimally, should the patient be challenged four times on each foot, six times on each foot or even more? How many challenges need to be missed to be considered an abnormal test? If the patient only needs to not feel the monofilament one time rather than two or three times the test will have a greater sensitivity but a lower specificity. Perkins evaluated monofilament testing utilizing a challenge to the great toe and found that the optimal sensitivity and specificity were obtained when an abnormal test result was defined as missing two or more challenges while a normal test was defined as the patient feeling either seven out of eight attempts or all eight attempts.[9] Specificity could be optimized by defining an abnormal test as missing five or more attempts. This approach led a dramatic drop in sensitivity if normal was defined as feeling only three or more attempts. Alternatively, keeping the definition of normal as feeling seven or eight attempts led to ambiguous results for those patients missing between two and four attempts.

Accuracy

Historically, the 10-g monofilament has been most widely used in the assessment of DPN. This size monofilament allows for the application of 10-g of pressure before buckling. Thus, by applying enough force to cause bending of the monofilament a maximum of 10-g of pressure is applied to the skin. Other sizes of monofilament such as a 1-g monofilament have been proposed as possibly more sensitive however, the 10-g monofilament continues to be routinely used.[8,11] Of course, diagnostic accuracy with a monofilament depends on a monofilament having accurate buckling properties. Studies investigating the accuracy of monofilaments buckling at the appropriate pressure revealed that not all monofilaments buckle at the expected pressure.[12] In addition, it is well recognized that with repeated use monofilaments fatigue resulting in buckling at lower pressure further reducing the diagnostic accuracy of monofilament testing.[12,13] Therefore, a physician in a busy clinical practice needs to make sure that a monofilament is not overused resulting in inaccurate results.

The sensitivity and specificity of the monofilament when used appropriately has been investigated and compared to the gold standard of nerve conduction studies. In a study by Perkins,[9] the sensitivity and specificity of the monofilament was calculated based on different diagnostic criteria. Subjects were tested eight times. When a normal assessment was defined as missing none or one test with a monofilament a sensitivity of 77% with a specificity of 67% was obtained. By using more stringent criteria requiring the patient to not feel more of the tests a greater specificity was obtained but at the expense of a lower sensitivity. The results are shown in Figure 2.

Figure 2.



Recreated from Perkins et al, 2001.[9]

As with all diagnostic tests, by adjusting the diagnostic criteria one can improve either the sensitivity or specificity but always at the cost of worsening the other.

A false positive, or type I error, is increased as the specificity of the test worsens. These false positives result in a lower positive predictive value. Thus, patients may either be inappropriately diagnosed with neuropathy leading to greater patient distress and possible utilization of resources the patient does not need. Alternatively, the physician may not be convinced of the diagnosis given the low positive predictive value and need to refer the patient for further confirmatory testing.

A false negative, or type II error, is increased as the sensitivity of the test worsens. These false negatives result in a lower negative predictive value. A patient with neuropathy but a negative result can therefore be missed or require additional testing with more sensitive testing equipment.

Other screening methods

While monofilament testing is recommended as a screening test, other screening tests are also recommended. These include the use of the tuning fork as well as assessment of reflexes. These tests are also limited in their sensitivity and specificity. Also, there is substantial variability in the ways that these tests are performed further limiting their accuracy. A meta-analysis of healthy people over the age of 60 without neuropathy revealed a significant decrease in vibratory sensation and ankle reflexes thereby decreasing the value of these tests in differentiating between patients with neuropathy and healthy older adults.[14]

Various survey tools have been created to formalize signs and symptoms in the results of testing to improve the diagnostic accuracy. One example of this type of testing is the Michigan Neuropathy Screening Instrument (MNSI). This instrument requires the patient to answer 15 questions and for the examiner to assess both feet for appearance, presence of ulcers, ankle reflexes, vibratory sensation and monofilament testing. While this tool has greater sensitivity and specificity than the monofilament alone, the amount of time needed to accurately utilize makes this tool most useful in clinical studies and difficult to implement in a busy clinical practice.[15,16]

Value of nerve conduction studies in diabetic peripheral neuropathy

Nerve conduction studies are recognized as the gold standard approach to assess peripheral nerve function. This evaluation includes testing for the presence of DPN.

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The American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation have jointly set electrophysiologic criteria for the diagnosis of DPN in clinical research.[17] These guidelines note that electrodiagnostic studies are sensitive, specific, and validated measures of the presence of peripheral neuropathy adding a higher level of specificity to the diagnosis.

Despite the fact that nerve conduction studies identify those patients with peripheral nerve damage due to DPN, there are a number of reasons why these tests are of limited use in clinical practice. As traditionally done, nerve conduction studies require a highly trained person, often a physician, to perform the test and the test typically takes a fairly long time to perform. This combination of the need for a highly trained person for an extended period of time results in a cost per test that is too high to be used as a routine office test. These same issues of time and expertise also mean that there is limited access to this test even if cost was not an issue. In addition, the need for a patient to schedule a separate visit at a neurophysiology laboratory removes the test from the workflow of the office visit further reducing its practicality.

NC-stat DPNCheck

The American Diabetes Association (ADA) Clinical Practice Recommendations states that all patients with type 2 diabetes be screened for diabetic peripheral neuropathy (DPN) starting at diagnosis and patients with type 1 should be screened starting five years after the diagnosis and then all patients should be screened at least annually thereafter using simple clinical tests. These practice recommendations acknowledge that the early recognition and appropriate management of neuropathy in patients with diabetes is important for several reasons including the fact that non-diabetic neuropathies may be present in patients with diabetes and are treatable as well as the fact that up to 50% of DPN may be asymptomatic and these patients are at risk for insensate injury to their feet.[18] While routine screening using simple diagnostic procedures such as the monofilament and tuning fork has been recommended it is recognized that there is a trade-off between the higher sensitivity and specificity of nerve conduction testing versus the need for an inexpensive, readily available, in-office test.

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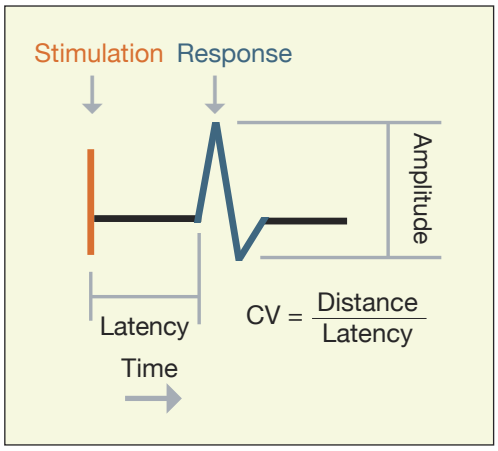
NC-stat DPNCheck was developed as an accurate, rapid sural nerve conduction study for the evaluation of DPN. The sural sensory nerve action potential has been shown to be a biomarker for DPN[19,20] so that a nerve conduction study of the sural nerve can act as a marker for DPN. Kong and colleagues demonstrated that nerve conduction studies can be analyzed by computer methods allowing for the automation of this type of study.[21,22]

The NC-stat has been shown to be a highly accurate device for detecting electrophysiologic abnormalities in the sural nerve of patients with diabetes. This technology has been shown to have a sensitivity of 92% and specificity of 82% when compared to traditional nerve conduction studies at identifying patients with DPN[20] with reproducible results.[22]

This technology has been incorporated into the NC-stat DPNCheck for the evaluation of DPN. The point of care device performs a sural nerve conduction study. Sural nerve action potential amplitude and conduction velocity (Figure 3) are measured in less than one minute and then displayed on the device allowing for an immediate and straightforward interpretation. The test may be performed by medical office staff and interpreted by a physician. This simplicity allows for its incorporation into a busy office practice and provides the physician with information while the patient is there for their visit.

Figure 3.



Why use a better test?

The clinical approach to the diagnosis of DPN for the past two decades has been a combination of history and physical exam along with simple screening tools such as the monofilament and tuning fork as outlined above. This approach has taken into account the degree of accuracy balanced against the difficulties of performing more definitive testing with nerve conduction studies. As discussed, current approaches have been shown to have limited accuracy in making a diagnosis of DPN[9] but the alternative approach with more sophisticated nerve conduction testing is impractical. With NC-stat DPNCheck, one can complement a clinician's current testing methods by utilizing the greater accuracy of nerve assessment with a test that is low cost and readily available. While utilizing NC-stat DPNCheck will lead to greater accuracy in the diagnosis of DPN, what advantages will that offer in clinical practice?

Making a definitive diagnosis

The majority of patients with diabetes who present with symptoms or signs of a distal symmetric polyneuropathy will have DPN as the cause. Yet, the diagnosis cannot be a foregone conclusion. Other etiologies need to be considered or risk missing significant and possibly treatable causes for the symptoms or signs. Other causes, such as B12 deficiency, alcohol abuse, neurotoxic medications, heavy metal poisoning, renal disease, chronic inflammatory demyelinating neuropathy, inherited neuropathies and vasculitis need to be considered.[18] For patients who present with pain or other parethesias in their feet, the differential diagnosis not only includes the various causes of neuropathy but also includes problems such as plantar fasciitis, bone spurs or other mechanical problem in the feet. These problems can sometimes be difficult to differentiate from neuropathy with any degree of certainty and yet their therapies are markedly different.

Performing a nerve conduction study with NC-stat DPNCheck can rapidly provide information to help make an accurate diagnosis. Because of the low type I error rate and hence high positive predictive value, an abnormal result helps confirm a diagnosis of symmetric peripheral neuropathy. Elimination of other causes of a symmetric peripheral neuropathy as outlined in the ADA guidelines allows one to make an accurate diagnosis of DPN. Once this diagnosis is made, appropriate therapy for DPN can be prescribed as needed.

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Alternatively, one is able to rule out a diagnosis of DPN if the result of the NC-stat DPNCheck is normal due to its very high negative predictive value. One can then reassure the patient that they do not have DPN and can recommend appropriate therapy to address the non-neurologic cause of the symptoms. In this way, one is able to avoid inappropriate prescribing of medications to treat DPN which will not provide relief and expose the patient to the risk of side effects and the expense of inappropriate therapy. Likewise, the proper etiology of the pain can be identified and appropriate therapy addressing the non-neurologic cause of the pain can be utilized.

Identifying disease burden

Landmark studies including the Diabetes Complications and Control Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that the risk of developing complications from diabetes is related to glycemic control.[23,24] Therefore, attaining good glycemic control has been a mainstay of diabetes therapy. More recent studies, including the Action to Control

Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Veterans Affairs Diabetes Trial (VADT) raised questions about the benefits of tight glycemic control in patients with diabetes of longer duration and at higher risk for cardiac complications.[25-27] A joint task force of the ADA and European Association for the Study of Diabetes (EASD) provided new recommendations for a glycemic target noting that a A1C needs to be individualized in patients based on duration of diabetes, age/life expectancy, comorbid conditions, known cardiovascular disease (CVD) or advanced microvascular complications, hypoglycemia unawareness and individual patient considerations.[28] Clearly, disease burden in terms of complications and life expectancy need to be taken into account. While we identify the presence or absence of retinopathy and nephropathy and then quantify their severity, the same approach has not been taken for neuropathy. As discussed previously, the current routine approach to diabetic neuropathy has poor sensitivity at identifying early diabetic neuropathy and only provides a qualitative rather than a quantitative assessment. Thus, a key piece of information regarding disease burden and the severity of complications is routinely absent.

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Patient example 1:

The patient is a 61-year-old Caucasian male with a history of type 2 diabetes for seven years. He is currently taking metformin 1000 mg BID and glyburide 10 mg BID. His most recent A1C was 7.3%. Over the past year his A1C has ranged between 7.0% and 7.4%. The patient follows a diabetic meal plan and exercises for 30 minutes four times each week. His body mass index is 27.5. His blood pressure is 128/78 on lisinopril 20 mg daily. He is also on statin therapy and achieving his cholesterol goals.

His dilated retinal exam two months ago revealed mild nonproliferative diabetic retinopathy. His urine microalbumin is normal. His most recent foot examination is normal with a monofilament and tuning fork. He has no history of cardiac disease.

His physician raised the issue of improving his glycemic control since his A1C has been greater than 7% for the past year. The physician discussed with him the fact that despite reasonable lifestyle therapy his current medical therapy is not allowing the patient to achieve ideal control and the possible need for additional medication. The patient noted that he is quite concerned about taking another medication especially because of the cost of therapy. He noted that he is feeling well and his diabetes has had a minimal impact on his health. His recent retinal examination showed only minor changes which his ophthalmologist assured him were of minimal concern at the present time.

While it is easy to recognize that this patient is not achieving his A1C goal, the challenge is to balance the cost of therapy (financial, impact on quality of life and possible side effects) versus the potential benefits in a patient who appears to be having minimal impact from his diabetes.

The patient is tested with NC-stat DPNCheck. One potential result is that the study is completely normal reflecting no evidence of diabetic neuropathy. Another possibility is that the patient has moderate nerve conduction abnormalities. While he still does have sensation in his feet, it is clear that the diabetes is having an advanced effect on his peripheral nerves.

The conversation which would follow regarding the impact of this patient's diabetes is likely to be significantly different depending on which NC-stat DPNCheck result was obtained.

Neuropathy as a predictor of cardiovascular disease and all cause mortality

Studies have shown a relationship between cardiac autonomic neuropathy and coronary artery disease.[29-31] In addition, more recent studies have shown a relationship between peripheral neuropathy and coronary artery disease.[31,32] Three recent major studies, ACCORD, ADVANCE and VADT, investigated the issue of whether intensive glycemic control resulted in improved cardiac outcomes.[25-27] These studies, while they differed in duration of diabetes and A1C target, did not show any benefit to intensive glycemic control. In fact, the ACCORD trial demonstrated greater mortality in those patients receiving intensive glycemic control. Post hoc analysis demonstrated the increased mortality in the intensive group occurred in those patients who did not lower their A1C within the first year.[33] Variables that might be expected to predict increased mortality such as age, duration of diabetes and prior history of cardiovascular disease did not correlate with mortality.

However, two factors that did predict increased mortality were if a patient reported a history of neuropathy and a higher initial A1C. In fact, a history of neuropathy nearly doubled the risk of mortality [hazard ratio of 1.95] whereas an A1C of > 8.5% had a hazard ratio of 1.64.[33] Hazard ratio is the rate of an adverse event occurring in the presence of a particular factor compared to the rate in the absence of that factor. Thus, patients with neuropathy with poorer glycemic control who cannot easily lower their A1C may identify those patients at increased risk from intensive glycemic control.

A recent study by Hsu and colleagues prospectively investigated the relationship between the presence of neuropathy as assessed by nerve conduction study and future mortality in patients with type 2 diabetes.[33] The presence of neuropathy increased the risk for all-cause mortality and diabetes-related mortality (death from diabetes, cardiovascular disease and cerebrovascular disease) significantly (HR = 4.88 and 6.58 respectively). When the risk from neuropathy was adjusted for other common risk factors (age, gender, blood pressure, smoking, history of cardiovascular/cerebrovascular disease, duration of diabetes, waist circumference, fasting plasma glucose, total cholesterol, hemoglobin, and creatinine) the hazard from neuropathy for all-cause mortality was 4.44 and for diabetes-related mortality was 11.82. So the presence of neuropathy increased the risk of diabetes-related mortality more than 10-fold when corrected for other risk factors.[34]

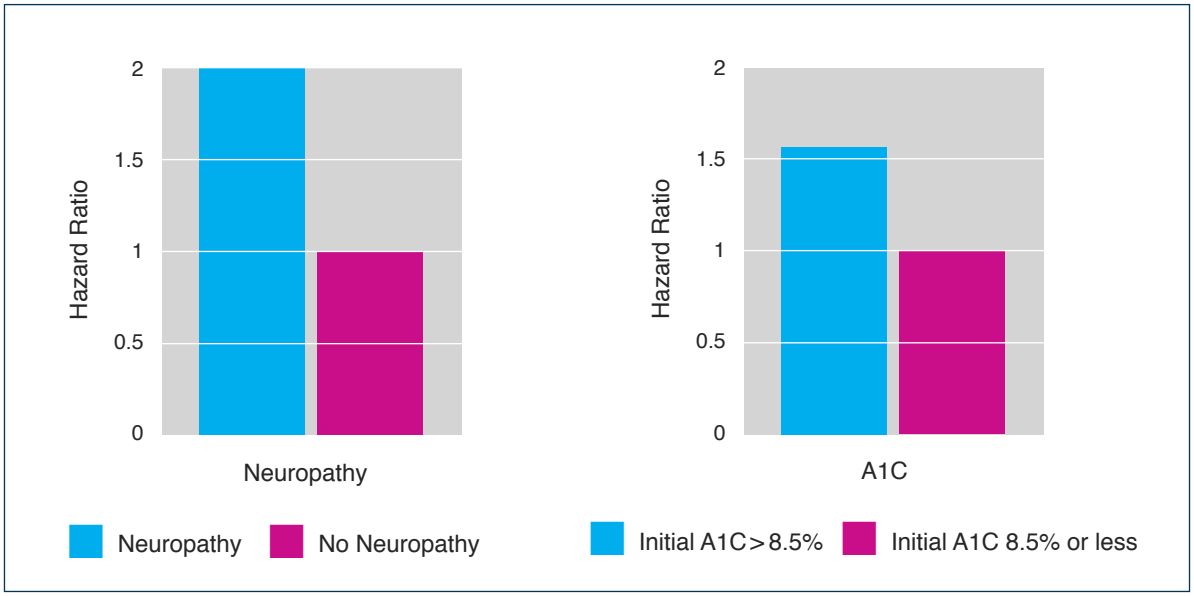
ACCORD Findings: [T]wo factors that did predict increased mortality were if a patient reported a history of neuropathy and a higher initial A1C. In fact, a history of neuropathy nearly doubled the risk of mortality [hazard ratio of 1.95] whereas an A1C of > 8.5% had a hazard ratio of 1.64.[33]

Whether neuropathy itself has a direct impact on mortality or if it is simply a marker for those patients who have a greater impact on their health from their diabetes is not clear. Regardless, the ability to rapidly identify those patients who are at greater risk for death is of paramount importance in order to risk stratify those patients and better assess the adequacy of their risk reduction therapy. In addition, comorbid conditions and life expectancy are key factors in assessing the goal for glycemic control as mentioned previously.[18]

Impact on self-care motivation

Studies have shown that there is a clear relationship between the psychological burden of diabetes and rates of self-care.[35] Indeed, fear of neuropathy and amputation are two of the major concerns of patients with diabetes and the presence of neuropathy has a significant negative impact on the quality of life for patients.[36,37] This relationship exists for multiple aspects of self-care including foot care.

Figure 4.



Hazard ratios of intensive glycemic control in the ACCORD trial based on the presence or absence of neuropathy or high initial A1C. Age, duration of diabetes and prior CVD did not correlate with mortality.

Recreated from Calles-Escandon et al, 2010.[33]

Studies have shown that those patients with symptoms of neuropathy or who perceive a higher risk of neuropathy are more likely to perform self foot-care.[38,39] In addition, patients who have had their feet assessed by their physician and have been educated about foot care are more likely to perform self-care of their feet.[38]

Patient peace of mind

Finally, it is easy to underestimate the value of providing piece of mind to patients based on normal test results. The following case helps illustrate this point.

Patient example 2:

The patient is a 37 year old woman with a history of type 1 diabetes for 26 years. Her diabetes has been complicated by very mild nonproliferative diabetic retinopathy, no nephropathy with a normal microalbumin/creatinine ratio. She has been on an intensive insulin regimen achieving an A1C consistently in the 7.0-7.5% range although has not been able to achieve a lower A1C without experiencing significant hypoglycemia. She is well educated regarding diabetes management as well as the complications from diabetes. She presents with a new complaint of occasional paresthesias and pain in her feet. She believes this could be related to being on her feet a lot and not always wearing the most supportive shoes. Her physical exam reveals normal sensation with a monofilament and tuning fork unchanged from her previous examination. Testing with NC-stat DPNCheck reveals

The patient takes great reassurance in knowing that she does not have evidence of DPN and admits that she has been very concerned about whether these symptoms marked the beginning of a significant complication.

normal results in both amplitude and conduction velocity. The patient is informed of the results of the testing and that given these normal results it is highly unlikely that she has DPN. The patient takes great reassurance in knowing that she does not have evidence of DPN and admits that she has been very concerned about whether these symptoms marked the beginning of a significant complication.

Conclusion

Screening for DPN with simple office tests such as monofilaments and tuning forks is a routine part of care for patients with diabetes. While these tests are simple, they are, unfortunately limited in their diagnostic accuracy. Nerve conduction studies are the gold standard for testing for DPN but are not practical in routine clinical practice. Newer technology in the form of NC-stat DPNCheck has now made available sural nerve conduction studies in routine clinical practice. By utilizing NC-stat DPNCheck one can now accurately diagnose DPN even at an early stage and hence have a more complete understanding of disease burden. DPN has been shown to be predictive of diabetes-related mortality as well as all-cause mortality. The ability to identify DPN allows for a better assessment of a patient's prognosis and in addition, the presence or absence of neuropathy may help predict who might benefit from more intensive glycemic control. Finally, there is also a significant role for providing patients with a more complete assessment of their diabetes status in order to help alleviate diabetes distress.

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