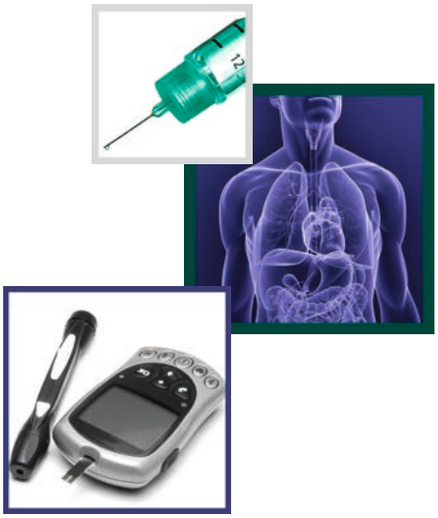
Reducing blood pressure can wait in new Type 2 diabetes patients



Delaying drug treatment to reduce blood pressure in new Type 2 diabetes patients may not have as many severe consequences as first thought. New research from the University of Chicago (IL, USA), published in the *Journal of General Internal Medicine,* has suggested that delaying the beginning of treatment for up to a year might not be harmful.

An obvious course of action when presented with a newly diagnosed Type 2 diabetes patient is to attempt to control their blood pressure to below the recommended level. However, a decision analysis performed by Neda Laiteerapong and colleagues at the University of Chicago has suggested that treatment can be delayed by a year with relatively minor consequences.

The study looked at two factors for judging the consequences of blood pressure treatment: lifetime complication rates for complications such as amputation, myocardial infarction and stroke; and quality-adjusted life expectancy (QALE).

"...delaying the beginning of treatment for up to a year might not be harmful."

The results confirm that a lifetime with uncontrolled blood pressure has significant negative consequences for patients, with 1855 complication events per 10,000 patients and a reduction in QALE by almost a year. However, a delay of a year before reducing blood pressure to controlled levels caused only 14 more complication events per 10,000 patients and a reduction in QALE by 2 days, in comparison with a lifetime of controlled blood pressure.

Although a year's delay has relatively few consequences, delaying the control of blood pressure for 10 years had significant negative consequences, with many more complications – particularly stroke and myocardial infarction – and a 142-day reduction in QALE.

While there are several causes for delays in treatment, for example, poor healthcare provision or the patient's reluctance to take medication, this is the first study to assess the negative impacts that a delay might have on the patient.

The authors conclude that a short-term delay in blood pressure control may be beneficial to the patient, allowing better focus on management strategies such as weight and diet control and lifestyle changes. However, a longer delay in controlling blood pressure, of 5 or 10 years, may have a more serious impact and would not be advisable.

– Written by Alisa Crisp

Source: Laiteerapong N, John PM, Meltzer DO, Huang ES. Impact of delaying blood pressure control in patients with Type 2 diabetes: results of a decision analysis. *J. Gen. Intern Med.* doi:10.1007/s11606-011-1951-y (2012) (Epub ahead of print).

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Ask the Experts

Study suggests inefficient and expensive tests may be used during neuropathy diagnosis

A recent study from the University of Michigan (MI, USA) has suggested that tests used to diagnose peripheral neuropathy, a common complication in diabetic patients, are more expensive and less efficient than they could be.

Brian Callagan (University of Michigan) and colleagues have used a medical insurance claims database to study the type and cost of procedures ordered during the diagnosis of peripheral neuropathy to determine whether the cost of diagnosis could be reduced.

The authors studied 15 tests commonly used during the diagnosis of peripheral neuropathy. The usefulness of each test can be inferred from the American Academy of Neurology recommendations that, as Callagan explained to *Diabetes Management*, "summarize the best evidence for testing in neuropathy."

Results from this study suggest that too many expensive and low-yield tests were used, rather than cheaper tests with a greater likelihood of a successful diagnosis.

Nearly a quarter (23.2%) of patients were given an expensive and relatively ineffective MRI scan, as opposed to a much cheaper and more effective glucose-tolerance test, which was only ordered in 1.0% of cases.

> "...too many expensive and low-yield tests were used, rather than cheaper tests with a greater likelihood of a successful diagnosis."

The problem is that there is "currently no standard approach to the evaluation of peripheral neuropathy", meaning that, as Callagan told *Diabetes Management,* diagnosis is "expensive" and "highly variable among physicians" and "we are likely not ordering the best tests".

Peripheral neuropathy, a condition involving damage to nerves, can lead to numbness and pain in limbs or problems with particular organs. At present, approximately 15% of Americans over the age of 40 years have been diagnosed with this condition.

As peripheral neuropathy can be caused by diabetes, the number of people undergoing diagnosis for peripheral neuropathy are likely to continue increasing as the number of diabetic patients increases. It is, therefore, important that the most efficient tests for diagnosis are used, particularly if they are cheaper than lower-yield tests.

According to Callagan, the researchers are now looking to "establish what are the main drivers of the expense associated with the evaluation of neuropathy." Hopefully, he says, "this will allow us to know which tests to focus on" in the search for a lower cost and more efficient evaluation of this increasingly common disease.

– Written by Alisa Crisp

Source: Callaghan B, McCammon R, Kerber K, Xu X, Langa KM, Feldman E. Tests and expenditures in the initial evaluation of peripheral neuropathy. *Arch. Intern. Med.* 172(2), 127–132 (2012).

Stem Cell Educator therapy might be a potential treatment for Type 1 diabetes

An exciting new development from the University of Chicago (IL, USA) has suggested that it might be possible to re-educate immune cells, allowing insulin-producing β-cells in the pancreas to recover and start producing insulin. This could lead to a potential treatment for patients with Type 1 diabetes.

Yong Zhao and colleagues at the University of Chicago performed a clinical trial aiming to reduce the autoimmune response to pancreatic islet β-cells by re-educating T cells with cord blood-derived multipotent stem cells.

Fifteen people underwent treatment during the open-label Phase I/II trial, which involved 12 patients with Type 1 diabetes and three control patients. The Stem Cell Educator therapy involves coculturing the patient's white blood cells with cord blood-derived stem cells for a few hours before returning them to circulation.

The effects of the therapy were judged by measuring the amount of C-peptide, a by-product of insulin biosynthesis, in circulation. In all diabetic patients, the levels of C-peptide increased 12 weeks after the treatment, an effect that was still seen 40 weeks later. As expected, this effect was not seen in control patients, in whom levels of C-peptide did not significantly change throughout the trial.

A long-term indicator of blood glucose level control, glycated hemoglobin, was also tested. This was shown to increase in stem-cell treated diabetic patients but not in control patients, suggesting that the treatment produces a lasting effect on metabolic control.

Importantly, two groups of diabetic patients were tested: those with residual

β-cell function, and so some level of insulin production before the treatment, and those with no residual pancreatic cell function. Both groups of patients showed increased production of insulin after therapy, demonstrating that the treatment works even after a complete halt in β-cell function.

"The Stem Cell Educator therapy involves coculturing the patient's white blood cells with cord blood-derived stem cells for a few hours before returning them to circulation."

Lead author Zhao told *Diabetes Management* that the data "provide powerful evidence that reversal of autoimmunity leads to regeneration of islet β cells," a very exciting finding as it suggests that a cure for Type 1 diabetes might eventually be possible.

Another important result of the study was a reduction in the dose of insulin required by patients after treatment. As Zhao says, this is evidence of the "improvement of metabolic control in long-standing Type 1 diabetes subjects" after Stem Cell Educator therapy.

The successful re-education of immune cells, both regulatory T cells and β-cell-specific T-cell clones, suggests that implications of this therapy stretch beyond diabetes treatment.

The authors "saw an improved autoimmune control in these patients," with markers, such as the proportion of regulatory T cells and levels of the cytokine TGF-β1, increased in patients after treatment. According to Zhao, "this principle may also be beneficial in the treatment of other autoimmune-related diseases."

"In all diabetic patients, the levels of C-peptide increased 12 weeks after the treatment, an effect that was still seen 40 weeks later."

The team are now looking to "optimize the protocol and improve the efficacy in a Phase II clinical trial".

– Written by Alisa Crisp

Source: Zhao Y, Jiang Z, Zhao T *et al.* Reversal of Type 1 diabetes via islet β-cell regeneration following immune modulation by cord blood-derived multipotent stem cells. *BMC Med.* 10(1), 3 (2012).

German Institute raises doubts over the extent of benefits of linagliptin treatment

The German Institute for Quality and Efficiency in Healthcare (IQWiG) has raised concerns over the supposed benefits of linagliptin treatment. At the beginning of January 2012 they claimed that the drug, which has been approved for treatment of Type 2 diabetes since August 2011, has not been adequately demonstrated to show benefit to patients.

Linagliptin is currently used to help control blood glucose levels in patients who cannot use, or do not respond well enough to, metformin as a treatment for Type 2 diabetes. However, the IQWiG has suggested that the manufacturer did not sufficiently follow instructions from the Federal Joint Committee (G-BA) – the decision-making body for clinicians and medical insurers in Germany. During the assessment of a drug, the G-BA requires the treatment to be compared with a specified comparator therapy in three distinct treatment situations.

"...the G-BA is conducting a formal commenting procedure to determine the extent of the added benefits of linagliptin treatment compared with other treatments."

However, the IQWiG has re-examined the evidence for linagliptin and has demonstrated that, during the efficacy study by the manufacturer, a different therapy was used as a comparator. The IQWiG claim that there is insufficient explanation as to why this change was introduced. The IQWiG also suggests that the manufacturing company has not provided adequate evidence to show an increase in benefit owing to linagliptin treatment even when compared with their alternative comparator in any of the three treatment situations.

In order to resolve this issue, the G-BA is conducting a formal commenting procedure to determine the extent of the added benefits of linagliptin treatment compared with other treatments.

– Written by Alisa Crisp

Source: Institute for Quality and Efficiency in Healthcare Press Release: www.iqwig.de/added-benefit-of-linagliptin-is-not-proven.1400.en.html?random=29bd8c

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Kidney problems in Type 1 and 2 diabetes may be predicted by TNF receptors

Two studies published online in the *Journal of the American Society of Nephrology* have shown a link between levels of TNF receptors 1 and 2 (TNFR1 and TNFR2) in diabetic patients' blood and their likelihood of developing kidney problems.

The studies, lead by Andrzej Krolewski from the Joslin Diabetes Center and Harvard Medical School (MA, USA), and a collaboration between many institutions, including the University of Warsaw (Poland) and the Juntendo University School of Medicine (Japan), measured levels of many different inflammatory factors, including members of the TNF pathway, in over 600 Type 1 diabetes patients and 400 Type 2 diabetes patients.

"...in both Type 1 and 2 diabetes, the number of people developing kidney problems was correlated with levels of circulating TNFR-1 and -2 more than 10 years previously."

The patients were followed over a period of 12 years to monitor any developing kidney problems, particularly end-stage renal disease, also known as chronic kidney disease.

The results of these studies found that, in both Type 1 and 2 diabetes, the number of people developing kidney problems was correlated with levels of circulating TNFR-1 and -2 more than 10 years previously.

In Type 1 diabetes there was a high correlation between TNFRs and renal problems. Those with higher TNFR2 levels when tested were three-times more likely to develop kidney problems in the next 12 years.

Half of Type 2 diabetics with the highest levels of TNFR1 went on to develop end-stage renal disease, in comparison with just 3% of patients with lower levels of the receptors.

However, circulating levels of the other factors that were measured, including the ligand for these receptors, TNF-α, did not correlate with future kidney problems in either cohort of patients, and levels of TNF-α were unrelated to the levels of its receptors.

Kidney problems are a common complication associated with diabetes, and as diabetes is a major cause of kidney failure in the US – approximately half of dialysis patients have diabetes – a diagnostic test for which patients are most likely to develop kidney problems could be very useful.

The study suggests that baseline levels of TNFR could be used in the clinic to provide an indication of potential kidney problems in diabetic patients. This might enable doctors to focus efforts on preventing the occurrence of renal failure, rather than treating patients once serious problems have developed.

"Those with higher TNFR2 levels when tested were three-times more likely to develop kidney problems in the next 12 years."

Krolewski told *Diabetes Management* that the group now hopes to "find a company that will develop our findings into a diagnostic test". Krolewski also hopes that their findings will encourage more studies on "the biology that underlies the association", which would hopefully will mean that "new therapeutic targets will be discovered", helping to prevent kidney disease in diabetic patients.

– Written by Alisa Crisp

Sources: Gohda T, Niewczas MA, Ficociello LH *et al.* Circulating TNF receptors 1 and 2 predict stage 3 CKD in Type 1 *Diabetes. J. Am. Soc. Nephrol.* doi:10.1681/ASN.2011060628 (2012) (Epub ahead of print); Niewczas MA, Gohda T, Skupien J *et al.* Circulating TNF receptors 1 and 2 predict ESRD in Type 2 diabetes. *J. Am. Soc. Nephrol.* doi:10.1681/ASN.2011060627 (2012) (Epub ahead of print).