Current Therapies for the Medical Management of Diabetes
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Question 1:

Treatment with metformin may confer risk reduction for which types of cancers? What would be the mechanism for this?

Response from Drs. Majumdar and Inzucchi:

Data from retrospective studies indicate that metformin use is associated with a lower risk of cancer and cancer-related mortality in patients with diabetes when compared to patients treated with other therapies, particularly sulfonylureas and insulin. One study showed a reduced risk for colon and pancreatic cancer, and others have suggested reduced risk for breast, liver, and prostate cancers, as well as lower overall mortality from cancer. However, a fair criticism is that those prescribed metformin may not be as sick or may fundamentally differ from those prescribed other therapies. Large prospective studies are lacking, although small studies do suggest potential benefits by way of surrogate markers; for example, reduced numbers of aberrant rectal crypt foci with metformin use, suggesting reduced risk for colon cancer. In laboratory studies and animal models of cancer, metformin has been shown to repress growth of colon, breast, liver, prostate, and other tumors. The underlying mechanism is unclear, but part of metformin’s action lies in suppressing cellular growth-promoting pathways such as mTOR, MAP kinase, and LKB1. Since metformin results in improved insulin sensitivity, insulin levels and other factors that are elevated in the setting of insulin resistance decline. Thus, metformin may offset some of the growth-promoting and potential mitogenic actions of insulin through insulin sensitization. Ultimately, human prospective trials will be needed to answer whether or not metformin truly lowers cancer risk and mortality, but at present there is at least a rational basis for the hypothesis.
Question 2:
What are some of the potential harms with tight glycemic control beyond episodes of hypoglycemia?

Response from Drs. Majumdar and Inzucchi:

If one were able to maintain glucose at normal levels, it would be difficult to foresee any adverse consequences of that alone; however, the means by which normal glucose levels are achieved and their associated side effects are the concern. One can consider weight gain from insulin, for example: if one gains 10–15 pounds while normalizing glucose, will this be considered a harm? For some it may. If a medication results in an increased risk of heart failure, then this will need to be balanced against the benefits expected from tight glycemic control. Therefore, the major harms to consider with tight glycemic control are those that potentially arise from the medications used, whether these include side effects, their costs, or the extent to which complex treatment regimens intrude into an individual’s personal life.

Question 3:
Are there any cost-effectiveness models estimating some of the lifetime clinical and economic effects of treatment of type 2 diabetes with these various combinations of medications?

Response from Drs. Majumdar and Inzucchi:

For insulin, metformin, and sulfonylureas, the answer is yes. The analyses favor treating diabetes as being cost-effective. Similar analyses for the newer and more expensive medicines are not readily available, and would also be more complicated since their cost would have to be weighed against not only their ability to lower glucose, but also their avoidance of side effects, such as hypoglycemia, and their potential to increase side effects unique to them.

Question 4:
Although you cite evidence for no obvious adverse consequences on the offspring of mothers who used metformin during pregnancy, what do we know about long-term effects of fetal exposure to insulin-sensitizing agents, such as developmental outcomes and metabolic effects?

Response from Drs. Majumdar and Inzucchi:

Not much, and so until more data become available, it still remains uncertain, although there have not been any obvious adverse outcomes identified. Again, one would need to weigh these concerns over those related to hyperglycemia on fetal outcomes. Certainly, it is reasonable to use diet and then the standard glucose-lowering therapy during pregnancy, namely insulin, as a next step in controlling hyperglycemia until more is known.

Question 5:
For patients with polycystic ovary syndrome (PCOS) who conceive while on metformin, is it worth continuing the metformin in hopes of preventing gestational diabetes mellitus?

Response from Drs. Majumdar and Inzucchi:

That is a very good thought. Given the previous question, when a patient develops hyperglycemia during pregnancy and then chooses metformin as a treatment, we accept a reasonable tradeoff in the known risks of hyperglycemia on fetal outcomes compared with the unknown long-term consequences of metformin after fetal exposure. Even though there is little evidence for harm at this point when used for gestational diabetes, one would have to consider whether it is appropriate to subject nondiabetic patients to metformin during pregnancy for diabetes prevention unless it is clear that preventing gestational diabetes has an outcome advantage over the standard approach to diagnosing and aggressively treating gestational diabetes.
Question 6:

In addition to measures such as exercise and dietary changes to effect weight loss, what is the role of drug treatment, such as with orlistat, in diabetic patients?

Response from Drs. Majumdar and Inzucchi:

If tolerated, safe, and affordable, treatments for weight loss should prevent and form viable treatment options for those with type 2 diabetes. Since weight loss typically results in improved glucose, lipid, and blood pressure levels, most therapies that can achieve sustained weight loss would be expected to improve diabetes and treatment outcomes. Currently available medicines are costly, have their own side effects, and ones that might be cheaper, such as orlistat, are limited in their use due to gastrointestinal side effects.

Question 7:

Where are we in terms of research on gene therapy or beta-cell replacement therapy for diabetes treatment?

Response from Drs. Majumdar and Inzucchi:

We think that the artificial or bionic pancreas (glucose continuous sensor driving an insulin infusion pump) will probably beat attempts at beta-cell replacement. Scientists have been trying for decades, either with islet cell or whole-organ pancreatic transplants, to replace beta-cell mass. At present, these techniques are only for selected individuals not able to adequately control their disease through conventional methods. Gene therapy is still decades away.