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Metformin For Prevention of Type II Diabetes

THE USE OF METFORMIN IN HIGH-RISK PATIENTS

Each month ReachMD XM 157 presents a special series. This month is Focus on Diabetes. Listen each hour at this time as we explore with American's top medical thought leaders for latest information on diabetes.

Diabetes ravages our patients and costs our medical system millions of dollars, is there a way to prevent the development of diabetes, especially in high-risk individuals. You're listening to ReachMD XM 157, The Channel for Medical Professionals. Welcome to the Clinician's Roundtable. I am Dr. Lee Freedman, your host, and with me today is Dr. Shelley Salpeter, Director of Medical Consultation Services at Santa Clara Valley Medical Center in San Jose, California, and Clinical Professor of Medicine at the Stanford University School of Medicine in Stanford, California.

DR. LEE FREEDMAN:

Thank you for being with us, Dr. Salpeter.

DR. SHELLEY SALPETER:

Thank you.

DR. LEE FREEDMAN:

Now, you've done a very interesting med analysis of the use of metformin for the prevention of type 2 diabetes, why is this an important issue for us?

DR. SHELLEY SALPETER:

Well, as you already mentioned that the prevalence of diabetes has been rapidly rising in the United States and this has been fueled by an epidemic rise in obesity and other metabolic risk factors. So the scope of the problem is really quite huge and is growing.

DR. LEE FREEDMAN:

And certainly is the primary care doctor, I am sure all primary care providers across the country see this in their everyday practice, metformin, why would we think metformin would be a good choice in prevention of diabetes?

DR. SHELLEY SALPETER:

Okay, so metformin is a biguanide agent that has been used in the treatment of diabetes for over 50 years now, so we know a lot about it. It works mainly through decreasing weight and reducing insulin resistance in patients with diabetes and it does very similar things for persons without diabetes and these beneficial effects could then help prevent the development of diabetes in the future.

DR. LEE FREEDMAN:

And I think metformin is having some effects of gluconeogenesis in the liver as well?

DR. SHELLEY SALPETER:

That's correct, so we don't really know the main mechanism of all of its beneficial effects because it does reduce weight and weight reduction itself can produce a lot of the beneficial effects that we see such as reducing glucose, insulin resistance, etc., so it's hard to tell really, which part of the mechanism is working towards the reduction of the development of diabetes.

DR. LEE FREEDMAN:

And certainly as you said it's been around for a long time, it's a mainstay of what we used for diabetics. In terms of safety, tell us a little bit about the diarrhea and renal function with metformin.

DR. SHELLEY SALPETER:

Yes, so as I said we've studied it for over 50 years now so it has been extremely well studied and actually it's quite safe. The main side effect of metformin is the gastrointestinal side effect such as diarrhea, a bloating and that's really its main dose dependent side effect. The one thing that we hear about all the time that we've been sort of taught to worry about is lactic acidosis. In fact, when you look at it, I did a med analysis of approximately 100,000 patient years of diabetic trials over the past 50 years and there was not a single case of lactic acidosis in the pooled analysis of approximately 100,000 patient years of diabetics, 50,000 patient years of metformin use.

DR. LEE FREEDMAN:

So, certainly very very safe. Is there a particularity of creatinine level or GFR at which we should, maybe, hesitate to use it?

DR. SHELLEY SALPETER:

Well, it's a good question. I use it in patients with renal insufficiency because I've been studying it for such a long time. If you look at all of the trials that have looked at metformin use over the past 50 years, they included a lot of patients with standard contraindications to metformin use which would include, as you mentioned, renal insufficiency. Also there are worries in terms of liver problems, elderly congestive heart failure, pulmonary disease, all of these are standard risk that people have been told to worry about. In fact, if you look at the trials, 96% of all of the participants in these trials had at least one of the standard contraindications to its use and there is still with not a single case of lactic acidosis. When you go back and you look at the history, you realize that it was a previous biguanide phenformin that was truly associated with lactic acidosis and in fact we now have no evidence whatsoever that metformin actually increases the risk of lactic acidosis in any of those groups of patients that were standardly considered to be contraindicated and in fact it doesn't even increase lactic acid levels, we also looked at that in our previous med analysis and the metformin does not increase lactic acid levels compared to placebo.

DR. LEE FREEDMAN:

That is very powerful and interesting evidence or data. So we have a medication that is very very safe and that in theory might work on some of the metabolic variables that lead to diabetes and we have certainly a huge problem, so tell us about this med analysis that you did, how did you look at studies what did you include?

DR. SHELLEY SALPETER:

Okay, our inclusion criteria were any randomized control trials in patients without diabetes that was at least 8 weeks long and compared metformin to placebo or no treatment and studied any of the metabolic parameters in the analysis that we looked at and the populations were very variable, but they all had a risk factor for diabetes, so no patient had diabetes and they all had at least one risk factor. The populations included patients with obesity, impaired glucose tolerance or insulin resistance, of positive family history of diabetes, hypertension, or peripheral vascular disease, dyslipidemia or abnormal lipids, then some syndrome that are quite common, one of them was metabolic syndrome and the other is polycystic ovary syndrome. Metabolic syndrome is basically a constellation of cardiac risk factors, together including abdominal obesity, hypertension, dyslipidemia, and insulin resistance and polycystic ovary syndrome is a very common condition affecting about 5% of women and that is associated with infertility and metabolic syndrome, so all of these populations were included in different trials that were included in the analysis.

DR. LEE FREEDMAN:

So, Dr. Salpeter we have patients with risk factors for diabetes that are included and what variables did you look at.

DR. SHELLEY SALPETER:

Okay, so we looked at a constellation of variables. This included weight or body mass index, lipids. We looked at HDL cholesterol, LDL cholesterol, and triglycerides. Then we looked at fasting glucose and fasting insulin and then from that we could calculate insulin resistance and then finally we looked at the incidents of new-onset diabetes.

DR. LEE FREEDMAN:

So, very important metabolic variables that we are all familiar with as well as the new onset of diabetes. Were you successful in finding a

number of trials that would fit this set of characteristics?

DR. SHELLEY SALPETER:

Yes, we did a very comprehensive search on Medline and we evaluated approximately 2000 studies, of which 92 trials were potentially relevant for our study and of those we found 31 randomized control trials that met our inclusion criteria.

DR. LEE FREEDMAN:

And what was the number of patients that this led to?

DR. SHELLEY SALPETER:

There were approximately 4500 patients in total and we followed over 8000 patient years of metformin.

DR. LEE FREEDMAN:

And when I see a med analysis I wonder how appropriate is the group studies together when they may be somewhat different. Was there a lot of heterogeneity in these studies?

DR. SHELLEY SALPETER:

Yes, certainly in terms of the population studied, there was a lot of heterogeneity. Once we looked at the results, we found that there was not heterogeneity in between the studies and we can talk about that shortly, but in terms of the studies themselves, the 31 studies were very different, some were very small, they ranged in size from 20 participants to over 2000 participants. They also ranged in the dose of metformin use, they went from 500 mg a day up to 2500 mg a day and then as I already mentioned there were a lot of different population studied, so we then did subgroup analysis looking at, for example, the difference in results for patients with polycystic ovary syndrome or no polycystic ovary syndrome for those patients, who were obese or not obese and for adults and children because all of these were included together in the med analysis.

DR. LEE FREEDMAN:

And were there differences in the outcome and conclusions based on those differences?

DR. SHELLEY SALPETER:

No, actually, the results were very very consistent across lines. In terms of the weight, which was may be one of the most important things that metformin does, there is a 6% reduction in body mass index compared to baseline and a 5% reduction compared to placebo or no treatment and that was very very consistent across all lines, so there was about a 5% reduction in weight for adults, for children, for those with polycystic ovary syndrome, for those without polycystic ovary syndrome and even for those who were not obese with the

lean patients, there still is about 5% reduction in weight or body mass index.

DR. LEE FREEDMAN:

Very nice and then how about some of the other results, how about the lipid parameters you looked at?

DR. SHELLEY SALPETER:

So that also was very nice in terms of its beneficial effect. There is a 5% increase in HDL cholesterol, which of course, is the good cholesterol, a 5% reduction in the LDL cholesterol, which gives you then, in terms of the LDL/HDL ratio, which is one of the risk factors that we look at, there was about a 10% reduction in the LDL to HDL ratio, and in addition, there was a 5% reduction in triglycerides.

DR. LEE FREEDMAN:

And then what might be the primary thing to look at, the blood sugars and new-onset diabetes, how did that come out?

DR. SHELLEY SALPETER:

Even in these nondiabetic patients, there was nobody, who had diabetes, there still was a 5% reduction in fasting glucose, a 15% reduction in fasting insulin and a 25% reduction in what we use as a calculated insulin resistance and along with that we found that over the course of the trial, there was a 40% reduction in the incidents of new-onset diabetes.

DR. LEE FREEDMAN:

That is very impressive. I know the shortest trial you said was 8 weeks, is this sustained, are some of the trials a bit longer?

DR. SHELLEY SALPETER:

Yes, it goes all the way up to 3 years, those with the longest of the trials was 3 years, the mean trial duration was 1.8 years, so close to two years on average, you can then calculate how many patients you would need to treat in order to prevent one case of diabetes and the number needed to treat here is 17, which is really relatively impressive.

DR. LEE FREEDMAN:

Very impressive compared to some of the other screening tests and other interventions that we do in medicine. So based on this impressive med analysis can we conclude now that we should be thinking about putting our high-risk patients on metformin or are we premature in making that assertion?

DR. SHELLEY SALPETER:

I personally believe that the benefits of the use of metformin is huge and it really is if you think about it, the only medicine that we have at all that has been shown to reduce weight while reducing cardiovascular risk factors, so it reduces weight in all the right ways. It's not like other medicines that would be increasing cardiovascular risk. We've had some weight reduction medicines that have even been taken off the market, but there is a medicine that reduces weight in all the right ways by also reducing lipids, abnormal lipid factors, insulin resistance, so it does it all in the right way and because of that and because it is maintained for such a long time, this is really of great magnitude in terms of any patient, who has risk factors for diabetes.

DR. LEE FREEDMAN:

I want to thank Dr. Shelley Salpeter who has been our guest as we've been discussing the use of metformin in high-risk patients. I am Dr. Lee Freedman. You've been listening to the Clinician's Roundtable on ReachMD XM 157, The Channel for Medical Professionals.

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