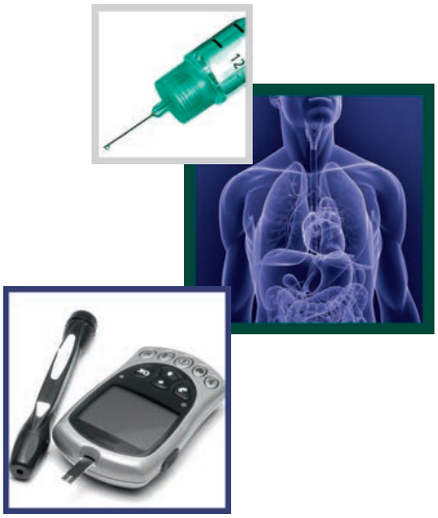

Pediatric diabetes management: past, present and future

Silva Arslanian* speaks to Sarah Freeston, Commissioning Editor: Silva Arslanian is the Richard L Day Endowed Professor of Pediatrics at the University of Pittsburgh School of Medicine (PA, USA). She is the Director of the NIH-funded Pediatric Clinical and Translational Research Center at the Children's Hospital of Pittsburgh (PA, USA) and Director of the Weight Management and Wellness Center, in addition to having been the principal investigator of the NIH-funded Diabetes Fellowship Training (T32) and Pediatric Diabetes Scholars Program (K12). Arslanian obtained her medical degree from the American University of Beirut (NY, USA) and completed her pediatric residency training at the same institution. She completed her fellowship in Pediatric Endocrinology at the Children's Hospital of Pittsburgh (PA, USA). Arslanian is funded by NIH, research foundations and pharmaceutical companies. Her research focus is the investigation of the pathophysiology of childhood Type 2 diabetes and its treatment. She has made major contributions to understanding insulin resistance during childhood growth and development, the metabolic syndrome, racial differences in insulin sensitivity and secretion, obesity and the risk factors for Type 2 diabetes in childhood. She was an investigator in the Diabetes Control and Complications Trial (DCCT) for Type 1 diabetes. She is the Pittsburgh principal investigator of a multicenter NIH-funded trial for Treatment Options of Type 2 Diabetes in Adolescents and Youth (TODAY). She is the Pittsburgh principal investigator of a multicenter NIH-funded trial for Restore Insulin Secretion (RISE), which is investigating the mechanism of correcting the pathophysiological component(s) of Type 2 diabetes with new therapeutic agents. She has occupied various national and international roles. She is a member of the Maternal and Child Health Study Section of the NIH, the Board of Directors of the Endocrine Fellows Foundation, the NCRR CTSA Consortium Child Health Oversight Committee (CC-CHOC), on the review board of American Diabetes Association, consultant to the NIH, the Office of Human Research Protection (OHRP), the CDC, US FDA, the Endocrine Society, the American Diabetes Association (ADA), International Study of Pediatric and Adolescent Diabetes (ISPAD), International Diabetes Federation (IDF), the European Medicines Agency (EMEA), the German Federal Ministry of Education and Research (BMBF), on the expert panel of the Dutch Medicines for Children Research Network (MCRN), and on the advisory board of several pharmaceutical companies. She serves as an editor, referee and reviewer for many journals. Arslanian has been an invited lecturer, key note speaker and chairperson at various international congresses and symposia in addition to being the recipient of several prestigious awards.

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Q What inspired you to pursue a career in pediatric endocrinology? Was this always a significant interest of yours?

I finished my medical school education in Beirut, Lebanon and when I initially applied to the USA for residency I did not have endocrinology in mind. I was applying for neonatology, but a good opportunity for pediatric endocrinology came up so, honestly, it was by default that I went into endocrinology. But I'm so happy that it happened that way! I love what I do. I joined the faculty at the University of Pittsburgh (PA, USA) and the rest is history.

Q How has your work progressed from your first studies to now? What are your current main areas of research?

When I was finishing my training, Pittsburgh was a well-renowned center for the epidemiology of Type 1 diabetes in children. Typically, when you stay where you train, you want to develop your own identity. So in my effort to establish an identity for myself, I decided to look into the issue of insulin resistance in diabetes. At that time, adult diabetics were shown to have insulin resistance and those studies prompted me to begin to evaluate if insulin resistance was also a problem in children with Type 1 diabetes, as there was a large Type 1 diabetes population of pediatrics in Pittsburgh. So that's how it started.

My first attempt was to assess insulin sensitivity using state-of-the-art *in vivo* methodologies, such as clamp experiments, which were only being used in adults, so I adapted them for use in pediatrics. Then I extended this to look into the problem of insulin resistance in the childhood population overall. One of my senior colleagues asked why I wanted to investigate a problem that was only present in adults. I explained that we don't become adults overnight! Just as we start crawling and walking then running, that's how health risk evolution over the lifespan may happen, and I thought it might be interesting to examine the presence of insulin resistance and its determinants in childhood. My studies have indeed progressed, the findings have been very interesting and every time we find the answer to one question, three questions come up that you need to find more answers to.

So, in a nutshell, my focus of research is childhood insulin resistance, risk for Type 2 diabetes and preservation of β-cell function in at-risk populations.

Q What has been your greatest achievement to date?

Academically speaking, I think I was probably one of the first researchers who recognized that we were seeing a different type of diabetes in children, and proceeded to investigate its pathophysiology. Approximately 15 years ago, pediatric endocrinologists started realizing that we were seeing children who were not typical of children with Type 1 diabetes, meaning these were obese adolescents who were presenting with diabetes that was not very severe. They would disappear from medical care, not take their medication and yet they did not suffer the serious consequences of severe hyperglycemia and/or ketoacidosis that children with Type 1 diabetes would. The latter group would deteriorate very fast if they don't take their medications, they could go into diabetic ketoacidosis; they could even die during a severe diabetic ketoacidosis episode. These obese adolescents with diabetes were very lax about their management and they were not succumbing to acute complications. A lot of us realized this, but I took it to the next level to investigate its pathophysiology and examine whether Type 2 diabetes in children is similar to adults. We published our findings, showing that obese youth with Type 2 diabetes have severe insulin resistance and impaired β-cell function compared with equally obese but normally glucose-tolerant peers. We took it a step further too, to show that potentially, the deterioration in β-cell function could be a lot faster than that observed in adults. The latter has significant ramifications in the treatment of youth with Type 2 diabetes, meaning that they may very quickly require multiple medications and/or insulin to control their diabetes. Furthermore, we demonstrated that obese adolescents with Type 2 diabetes have a premature aging of their cardiovascular system, heightening their risk for macrovascular complications.

Q What has been the greatest advance that you have witnessed during your time in the field?

I think we have made major strides in the last 10 years in terms of recognizing that Type 2 diabetes in children is really a problem, at least in North America. Approximately 12 years ago when I used to give lectures in Europe, my European colleagues said that Type 2 diabetes in youth was only a problem in North America; but then later on, they started seeing that it was

invading European territories too. Of course childhood Type 2 diabetes is present in Asia and it is highly prevalent in the Arabian Gulf. I think the awareness that Type 2 diabetes is not only unique to the USA and that the rest of the world is catching up has been a major advance. In North America, great advances have been made in realizing which therapeutic approaches may or may not work, and that was mostly the result of the TODAY study [1]. The TODAY study will also provide tremendous knowledge about the changes in insulin sensitivity and secretion consequent to therapy, as well as the diabetic complications in these patients.

Q What are the aims of the multicenter TODAY trial & what have been the most significant findings to date?

TODAY stands for Treatment Options for Type 2 Diabetes in Adolescents and Youth. It was a multicenter study that randomized approximately 699 overweight and obese adolescents, aged 10–17 years old, who had Type 2 diabetes for less than 2 years duration. The purpose was to assess which of three different therapeutic approaches was best in inducing glycemic durability and/or preventing treatment failure. The interventions included metformin alone, metformin plus rosiglitazone, which is a very potent insulin sensitizer, and metformin plus intensive lifestyle intervention. Treatment failure was defined as acute metabolic decompensation or sustained elevation in HbA1c above 8% for 6 months.

One has to remember that until the results of TODAY, and even until now, there is only one oral antidiabetic agent approved in pediatrics, which is metformin, and this was the result of a 16-week trial only, which showed that metformin was effective compared with placebo in newly diagnosed kids with Type 2 diabetes to lower their HbA1c [2].

So what the TODAY trial found was that among the three therapeutic approaches, failure rates in general were higher than in adults. Of course, the comparison with adults was based on what is published about adult Type 2 diabetes in the literature. Thus, it was somewhat surprising that children were not responding as well as adults, but may be not so unexpected because we already had some data that their β-cell deterioration could be more severe than adults.

In TODAY, metformin plus rosiglitazone was the best approach in preventing failure. The failure rate of metformin plus rosiglitazone was 38.6% and in the metformin-only group, it was 51.7%. Therefore, more than half of the children on metformin failed; there was no durable glycemic control on metformin. The median duration for failure was around 11 months.

The other surprising finding was that metformin plus lifestyle was intermediate, so the intensive lifestyle component did not really add any benefit to metformin. When I say intensive, lifestyle coaches met with the patient and the families on a weekly basis during the first 6 months to help them to overcome barriers, change their eating habits, improve their activity levels and lessen sedentary behavior. They then met every other week for another 6 months and then monthly thereafter. Despite this intensive behavioral/lifestyle intervention, we didn't see magical results; we didn't see that the group who was taking metformin plus lifestyle achieved remarkably greater weight loss or greater sustained glycemic control.

Q How did these conclusions influence diabetes management?

Rosiglitazone worked really well with metformin, but unfortunately, it has been ousted because of its potential negative cardiovascular effects and bone fractures in postmenopausal women. Rosiglitazone is not approved in the USA or other countries for use in children with Type 2 diabetes. Despite the results of TODAY regarding the beneficial outcome of metformin plus rosiglitazone, it is going to be very difficult to use rosiglitazone in pediatrics.

Therefore, we're left with metformin and lifestyle. Lifestyle did not prove to be as promising as one hoped but, again, we have to remember that adolescents are very different from adults. In the DPP, lifestyle worked [3]. But this was in adults, many of whom were retired. They could commit time to intensive behavioral/lifestyle management. The adolescent period is associated with rebellious behavior, feelings such as "I'll do as I wish" and "I don't have to listen to my healthcare provider or parents", so everything that we try to implement contradicts with the normal psychological development of adolescents. When they've been obese for the last 15/16 years, it's very difficult to change that, especially during the critical period of adolescence. So, honestly, for those of us who lived with those kids, and I say 'lived' because we became very familiar with them, the result that lifestyle was not the

magic bullet, was not surprising at all because we saw what these children and their families were doing. So are the TODAY results persuasive enough for one to implement intensive lifestyle at this moment? Probably not, because it didn't prove to be effective. More importantly, it is very costly, difficult to apply in the clinical setting, and institutions and insurance companies are not willing to fund and support such efforts. However, more creative lifestyle interventions, making use of biotechnology, should be examined in case they turn out to be more effective, but I remain skeptical.

For the moment, we're left with metformin, on which more than 50% of the patients failed. Many pharmaceutical companies are now developing, or have developed, new drugs that are already approved in adults, but they need to be approved in pediatrics. So the pharmaceutical companies are flocking to centers or physicians who provide care to adolescents with Type 2 diabetes, to test the efficacy and safety of these new drugs.

We definitely need new pharmacotherapies in Type 2 diabetes. The development is going to be slow because typically, companies don't get into the pediatric field until the drug is officially approved in adults. Another problem is the delays due to various regulatory agencies' requests for protocol modifications to get approval in various countries. Lastly, even though the number of children with Type 2 diabetes is increasing, it is not of epidemic proportion, so if you want to test five different new drugs, there isn't a sufficient patient population to test on; most companies are really struggling to find the necessary number of children with Type 2 diabetes for their study.

Q How does obesity influence the progression from prediabetes to diabetes in children?

I think obesity probably influences the progression, not necessarily from prediabetes to diabetes, but from normal to dysglycemia or from normal to prediabetes and its progression. The major determinant is genetic predisposition. If you're genetically at risk, but you are normal weight, physically active and you eat healthily, the genetic predisposition will not manifest clinically. However, once your lifestyle deteriorates, then that genetic predisposition will surface. A while back, we performed studies in normal-weight healthy children who came from families who had Type 2 diabetes versus normal-weight children who came from families who did not have Type 2 diabetes. In the former group, we could demonstrate that the metabolic derangements conducive to Type 2 diabetes were present, meaning, they were more insulin resistant and they had impaired β-cell function compared with the latter group, despite the fact that they were normal weight. But if you take that metabolic predisposition and you confound it with obesity, then that's going to break the camel's back and that is what's happening. Once children become obese, their genetic risk and predisposition to diabetes begins to manifest. Thus, obesity pulls the trigger on a genetically loaded gun, such that with increasing obesity, the risk of progression from normal glucose tolerance to abnormal increases. However, the progression from prediabetes to Type 2 diabetes appears to be mostly the result of a failing β-cell to compensate for the obesity-driven insulin resistance. When you're obese, if your β-cell is working well, it will compensate for the insulin resistance and keep on producing enough insulin to maintain glucose homeostasis. But once the β-cell starts deteriorating, not just a mere fact of overload, but due to genetic predisposition and other yet unknown factors, then it's not able to increase its insulin secretion to levels needed to overcome the insulin resistance; at that point glucose levels start deteriorating from normal to prediabetes. With the continued deterioration in β-cell function, one ultimately develops Type 2 diabetes.

We had the opportunity to follow a few children longitudinally, and showed that the critical factor in the ultimate manifestation of Type 2 diabetes is β-cell failure. There is now a lot of ongoing effort to try and see how we can prevent the progressive decline in β-cell function or how we can reverse the process. So that's where we are.

Q How does treating diabetes in children differ from adults? What are the most significant challenges?

Typically, treating children has additional layers of complications. For example, children are dependent on their parents. Research after research shows that if the parents are invested in the child, then the outcome is better. If the parents are not invested for whatever reason, for socioeconomic reasons or maybe they're too busy, you're not going to be able to achieve the same sort of success working with a child alone because the child is dependent on the parent.

The other complicating factor is that as children go through puberty or through the period of adolescence, there are major psycho-behavioral changes that contrast terribly with everything we tell them to do when it comes to diabetes care. For example, independence is very important for adolescents; they have absolutely no independence when it comes to their diabetes care, as they're dependent on their parents or drug or medical team telling them what to do and when. The other thing is privacy, teenagers are very private. There's no privacy when they come to see the physician or nurse every 3 months. Then some have the attitude that they're invincible and that nothing hurts them so they think they can stop taking their insulin, well, this goes against everything we tell them. We tell them that if they don't take their insulin, they will go into diabetic ketoacidosis, if they don't eat properly, their lipids will go up, and so on. There's a tremendous contrast between the beliefs of adolescents versus what the medical team suggest for controlling diabetes, and that creates a conflict. And then, of course, you have to deal with the parents too; your patient is not only the child but also the child's parent. Therefore, for all these reasons, it makes it more challenging for pediatricians dealing with children.

Q In summary, where do you think the main focus of your research will be over the next 5 years?

The main focus is probably going to be in probing how we can halt the relentless decline in β-cell function. This is critical because if you can do it in already-established Type 2 diabetes, then you can sustain glycemic durability. If you can do it in somebody who may progress from prediabetes to Type 2 diabetes, then you can prevent progression to Type 2 diabetes, or you may even be able to reverse them to normal glycemia.

Also, over the last 20 years, one aspect of my research has been in trying to understand racial disparity in the risk for Type 2 diabetes. The results of TODAY show that there is a racial disparity in response to treatment too. So, in an era where individualizing therapy is of great interest, one has to investigate the reasons behind such disparities, not only for risk, but as importantly how best to treat Type 2 diabetes in different ethnic groups. Another area of progress in research that needs to be accomplished, is the complications of Type 2 diabetes in youth: both macrovascular and microvascular. I suspect macrovascular complications are going to be much more problematic in these obese youth because of the added burden of obesity-related comorbidities. Lastly, there is a need to find new pharmacotherapeutic agents, not only for diabetes, but also for obesity. I think we need safe and effective therapeutic agents that can produce clinically significant improvement in weight and in BMI in the face of the escalating rates of obesity.

Q What challenges remain in the field of pediatric diabetes as a whole?

The biggest challenge, in my opinion, is changing behavior. There's no question that it's very difficult to have diabetes. The daily demands are enormous. But there are some patients who are very successful with their diabetes management, whereas others are not. So the question is how can we translate whatever causes success in those patients to those who are not successful? A lot of it boils down to adherence to therapeutic recommendations, to changing behavior and lifestyle to healthier ones, but it's very tough. I don't know what the answer is: but defiantly, there's still a lot of work to be done.

Financial & competing interests disclosure

S Arslanian has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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