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ANDROGENS: Interview with Paresh Dandona, MD

Interview by Abraham Morgentaler, MD

Dr. Abraham Morgentaler: On behalf of *Androgens: Clinical Research and Therapeutics* I am delighted today to have the opportunity to interview Dr. Paresh Dandona, Distinguished Professor of Medicine at State University of New York in Buffalo, and one of the leading figures in research and scientific discovery regarding testosterone and diabetes. Dr. Dandona, it is a pleasure to be with you today.

Dr. Paresh Dandona: Well, thank you very much. It is a pleasure to be with Abe.

Dr. Morgentaler: Please tell us how you got started investigating the relationship between testosterone and diabetes.

Dr. Dandona: It is a very interesting story, Abe. And this is what clinical medicine is all about. The excitement that you never know what you are going to see tomorrow. So all my interests since 1975, when I started my career in diabetes, in London, England, till 1995 when I started this center single handed in upstate New York, which is now the largest diabetes endocrine center in upstate New York, were in vascular disease, atherosclerosis, and related issues. And then in 1998, something amazing happened, which was the arrival of sildenafil (Viagra) on the scene, and urologists in Buffalo started prescribing Viagra as if there was no tomorrow. And if you remember, the original *New England Journal of Medicine* article had shown that in this condition of erectile dysfunction (ED), where there was no treatment till then, 70% to 75% responded to Viagra, which was an amazing statistic.

However, the fact that in the diabetic patients, and this was an article published in *JAMA*, later the same year, the positivity rate was only ~45% to 50%. And you can understand that because diabetic patients have neuropathy, vasculopathy, and all those problems. So these patients who were nonresponders got referred to me. And being an endocrinologist, I did systematic investigations, and what I noticed was that almost every one of the patients who had been referred to me by urologists with diabetes had a low testosterone to the extent that I was worried about the laboratory assay. So, I asked the laboratory, "Hey guys, is your testosterone assay working?" They responded, "Okay, let's do an assay analysis of your patients versus the rest." They came back to me 2 weeks later, "It's only your patients who have the low testosterone values."

Dr. Morgentaler: What an interesting observation.

Dr. Dandona: Indeed. It became quite clear that every time I was looking at a diabetic patient with ED, it would turn out that their testosterone was low. In the year 2000, I was joined by a fellow, Sandeep Dhindsa, who is currently the Chief of Endocrinology at Saint Louis University in St. Louis. I asked Sandeep to measure testosterone in all of our new referrals. This led to the first article in the *Journal of Clinical Endocrinology and Metabolism* in 2004 showing that one-third of type 2 diabetic patients had low testosterone concentrations. The patients also had low luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations. However, the response of LH and FSH to GnRH stimulation was normal. This allowed us to conclude that the defect was in the hypothalamus and not in the pituitary. Yet I still wondered, how can an additional endocrine syndrome exist within an endocrine disease? But then 2 years later, a British group from Sheffield, led by Hugh Jones confirmed that. Groups from Brazil, Australia, and then Italy confirmed it. So, it was clearly a global condition and type 2 diabetes was associated with the hypogonadal state.

Dr. Morgentaler: What did you do next?

Dr. Dandona: The first question I asked as a diabetologist was, is it dependent upon the quality of control of

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diabetes, or is it dependent upon the duration of diabetes? And neither of them was true. The only correlation we found was with body weight, body mass index (BMI). So the next question was, is obesity itself a cause of hypogonadism? I then approached the people who had done the hypogonadism in males (HIM) study. The HIM study was a study to look at the prevalence of hypogonadism in the society in general. They had done an investigation of testosterone levels in patients attending primary care clinics. About 2600 patients had their blood samples taken on the same day and were assayed for testosterone. When we got these data and analyzed them, clearly obesity itself was the cause of hypogonadism because 25% of obese men in that study had low testosterone concentrations. When we looked at the patients with diabetes in that study, they had an additional ~10% risk of hypogonadism. Thus, one-third of type 2 diabetic patients and one-fourth of obese nondiabetic patients clearly had the syndrome of hypogonadism.

Dr. Morgentaler: Paresh, if we were to draw a Venn diagram, a plot of individuals who are obese, individuals who have diabetes, and individuals who have low levels of testosterone, there would be a lot of overlap. Right?

Dr. Dandona: Absolutely. No question.

Dr. Morgentaler: And so the question I have for you is how in your mind do you think of these three conditions and how they are related: obesity, diabetes, and testosterone.

Dr. Dandona: Right. So I will come to that. As we evolve through the story, some of your questions will be answered as we go on. But the other important part is that when we published the very first article in 2004, I was looking for some guidelines in research as to where these thing could have been done. And some epidemiological studies had been on the west coast by Elizabeth Barrett-Connor, the well-known epidemiologist. And she had shown previously that diabetes and obesity were associated with low testosterone, but they had not defined this as a clinical syndrome. It was just an epidemiological observation that testosterone tends to be low, and they had not measured total and free testosterone.

But in terms of mechanism and etiology, the article that hit me was from Ronald Kahn's group from Joslin Clinic published *Science* in 2000 where they had knocked out the neuronal insulin receptor. So it was a neuronal insulin receptor knockout mouse. And what they were trying to show was that knocking out insulin receptor in the brain would lead to insulin resistance. That it did. But what was shocking and alarming was that these animals with an insulin receptor knockout in the brain had hypogonadotropic hypogonadism, exactly the kind of syndrome that we had described. The low testosterone was not due to primary testicular abnormality. They were due to abnormalities in the hypothalamus because when we did stimulation tests with GnRH, the results were perfectly normal. So pituitary was okay. Further studies came out to show that it was possibly GnRH secretion, which was altered. That is what led to the syndrome in the mouse after insulin receptor knockout. In our patients with type 2 diabetes and obesity, both of which are insulin-resistant states, there could be a defect in GnRH secretion. And so there was a match up there. I shall come to the issue of insulin resistance again a little later as we move into treatment with testosterone.

Dr. Morgentaler: Very good. Why don't you tell us about that right now?

Dr. Dandona: Okay. But before I go there, I just want to comment on type 1 diabetes.

Dr. Morgentaler: Alright.

Dr. Dandona: So that was the next question we wanted to embark on and we compared type 1 diabetic patients with type 2 diabetic patients. We demonstrated that this syndrome was confined to type 2 diabetic patients alone unless the type 1 diabetic patient was obese. Clearly then, obesity was mediating the syndrome. Next question then was, what about children? Do they have this syndrome as well? Now that we have an increasing population of type 2 diabetic children, we compared type 1 diabetic children with type 2 diabetic children. Again, what turned out was again startling. In this article published in *Diabetes Care*, we showed that >50% of type 2 diabetic children were hypogonadal, whereas those with type 1 diabetes were not. Again, there was a correlation with body weight because type 2 diabetes in children also is obesity related. This led us to conduct a study in obese adolescent males aged 14 to 20 years. Obese males had testosterone concentrations that were 50% lower than those in normal boys. Free testosterone concentrations were lower in the obese patients by one-third. Testosterone concentrations were inversely related to BMI.

Dr. Morgentaler: Paresh, let me return to my earlier question. What can you tell us about the

inter-relationships between obesity, diabetes, and low testosterone? Men with advanced prostate cancer, for example, are usually treated with androgen deprivation, and these men routinely gain weight, and some of them will develop impaired glucose control. Is it obesity, low testosterone, or some combination of both that predisposes to the glycemic dysfunction? Conversely, recent studies indicate that testosterone therapy reduces fat mass and results in improved glycemic control. So the question is, is it the gain of fat that predisposes to diabetes and to the lowering of testosterone, or is it the low testosterone that is predisposing to the diabetes and the gain in fat?

Dr. Dandona: An excellent question. In fact, it is a vicious cycle: obesity triggers insulin resistance and low testosterone and low testosterone promotes obesity and increase in adiposity. We are currently doing a prospective study on androgen deprivation therapy, and we have just obtained a small grant to get some preliminary data from and hopefully it will expand to a large mechanistic study. The treatment of prostate cancer with androgen deprivation leads to greater adiposity and a greater level of insulin resistance and diabetogenicity and with it, of course, again, an increased cardiovascular risk. So that is one area that we are investigating currently, but we do not have specific answers to, but the rest of the data are already there in the literature.

Dr. Morgentaler: And do we know the biochemical or cellular mechanisms by which this occurs?

Dr. Dandona: Yes. When the NIH gave us a handsome grant to look into testosterone replacement, we had a whole lot of hypogonadal type 2 diabetic patients. Half of whom got testosterone, the other half got placebo for a period of 24 weeks, ~6 months. And what we demonstrated in this study was very interesting. Although there were some preliminary data previously there, but this study made it absolutely clear. Number 1, the hypogonadal type 2 diabetic patients were more obese than the eugonadal type 2 diabetic patients. Number 2, the fat biopsies that we obtained from them showed that these patients had specific molecular defects at the level of the insulin receptor beta subunit, IRS-1, AKT2, and GLUT4, the glucose transporter-4 that is responsible for glucose transport in adipose tissue, and in skeletal muscle. Each of these genes was underexpressed by ~20% to 30%.

We then did the euglycemic hyperinsulinemic clamps, which is the standard way of measuring insulin resistance. Lo and behold, the obese type 2 diabetic patient with hypogonadism had an insulin resistance 35% greater than that of the eugonadal type 2 diabetic patient. So not only was there a 35% reduction in insulin sensitivity, there was also diminished insulin signal transduction at the molecular level. Over a period of 24 weeks that we treated these patients with testosterone, all of these elements related to insulin resistance mathematically reversed. So the insulin sensitivity came back to the levels that the type 2 diabetic eugonadal patients had, and with it all the defects at the molecular level that were subnormal normalized. So clearly, the whole situation is rather precise and I feel certain, therefore, that when we do the androgen deprivation therapy study, we will be retracing these mechanisms as we look at their fat biopsies and so on as we go on.

A few additional studies followed from that study. Number 1, we looked at the expression of androgen receptor, estrogen levels, estrogen receptor, and aromatase in the adipose tissue. And what emerged again was very exciting. The hypothesis was that in these hypogonadal patients, the expression of the androgen receptor would be increased because that is the teleological way we think of it. Nature would compensate for the low testosterone. However, it turned out the other way around: not only was the testosterone concentration low, but the expression of the androgen receptor was also diminished. So what you will get is a double whammy. Then we looked at estradiol levels, they too were low. So if you are hypogonadal, your estradiol concentrations fall. Estrogen receptor expression was also diminished. Last but not the least, the expression of aromatase enzyme, which converts testosterone to estradiol, was also significantly diminished. After 6 months of administration of testosterone, all of this, again, mathematically reversed back to normal. So again, this was very interesting that we had a situation wherein actually the hormonal lack was associated with a lack of the receptor too, and when you corrected the hormone concentration, the expression of the receptor also normalized.

Dr. Morgentaler: Fascinating.

Dr. Dandona: The other observation I just want to mention in this study was the fact that the baseline without testosterone or low testosterone was associated with metabolic inflammation, which too got suppressed with testosterone administration.

Dr. Morgentaler: Paresh, you have been involved in a number of studies involving testosterone therapy in diabetic patients or prediabetic patients. What can you tell us about those studies?

Dr. Dandona: In 2019, an article appeared from Farid Saad's group in Bremerhaven in Germany, which demonstrated that testosterone therapy in prediabetic patients with obesity over a period of a decade or more led to reversal of prediabetes. This was really exciting because it was consistent with what we had shown mechanistically at the molecular level. To have somebody provide data to confirm this, really, I was over the moon, overjoyed that clearly that testosterone works over a long period, too. They also had data showing that these patients had steady loss of their body fat, and improvement in insulin resistance, and with it, the reversal of prediabetes. That was exciting! In the arm without testosterone therapy, the prediabetes deteriorated enough to manifest diabetes in a significant proportion of those patients.

Dr. Morgentaler: For the nonexperts in diabetes, how is prediabetes defined?

Dr. Dandona: HbA1c is the simplest measure. An HbA1c of between 5.7% and 6.4% is prediabetes. As soon as you get to an HbA1c of 6.5%, you have diabetes. Now, there are a couple of other things I just want to mention here because they are extremely important in relation to testosterone. For decades, we have known that testosterone administration builds up muscle. And of course you had articles in early 1990s that showed that testosterone administration in supranormal amounts enhances skeletal muscle. But nobody really knew the exact molecular mechanisms underlying this. So when we had our NIH-funded study wherein we had done 6 months of administration of testosterone, we had demonstrated that there was a loss of $\sim$3.5 kg of body fat, largely from the abdomen. At the same time, the total body weight had not changed because 3.5 kg of muscle had built up.

When we performed muscle biopsies in these patients, we investigated in detail the factors that could have led to the growth of the muscle. So just briefly, without getting too technical, IGF-1 concentration increases with testosterone administration. That is an old action of testosterone that is well known for a long time, but we confirmed that. In addition, fibroblast growth factor 2 (FGF2), known to promote muscle growth in mice, increased sharply, both in plasma and in the muscle. Not only that, FGF2 receptor also come up sharply in its expression in the skeletal muscle. Now, the other interesting thing that happened was the two major factors that inhibit muscle growth, myostatin and something called MRF4 were suppressed by testosterone.

So clearly now, we have a much better understanding of why muscles grow under the influence of testosterone. This is the first comprehensive report of its kind. It will need to be confirmed in future by others, and of course, to be developed further. What our study still misses is a clear-cut mechanism underlying the loss of adipose tissue. I would love to be able to making some discoveries there, but they are yet to come, but this is an empty space that can be occupied by anyone who gets into that area.

Dr. Morgentaler: So if I am understanding you correctly, we are able to put our finger on suggestive mechanisms by which testosterone improves lean mass or muscle, but we do not know enough yet about mechanisms by which it diminishes fat. Is that right?

Dr. Dandona: True, absolutely true.

Dr. Morgentaler: This is a wonderful scientific story, Paresh.

Dr. Dandona: Let me add another little very exciting piece here. As a part of the NIH study then, we went on to do yet another investigation into hematocrit because we have known for ages that testosterone stimulates hemoglobin synthesis. We looked at these patients who were hypogonadal and they had significantly lower hemoglobin levels, although not such that they would be called anemic. When we gave them testosterone for 6 months, the hemoglobin levels came up. So the next question was, what is the underlying mechanism? And at that time, what we knew already from Shalender Bhasin's study was the fact that testosterone suppressed a protein called hepcidin from the liver. It is a proinflammatory agent that suppresses something called ferroportin, which is the transport molecule for iron for absorption from the gut on the one hand and for the release of iron from storage inside the body on the other hand. The storage sites are reticuloendothelial cells because they do the red cell killing when they are aged and then have a store of irons, which has to be released.

What we demonstrated was that in the hypogonadal patients, hepcidin levels were high, ferroportin expression was low, and transferrin, the plasma

protein that transfers iron to the utilization sites, was also low. Moreover, the transferrin receptor, which takes up the transferrin-bound iron to synthesize hemoglobin at that site, was also low. Lo and behold, testosterone reversed it all systematically, hepcidin concentration fell and ferroportin expression increased, transferrin increased, and transferrin receptor increased. And with it, the total stores of body iron, as reflected in ferritin, fell because they were now being utilized for hemoglobin synthesis that was not happening in the hypogonadal state. These mechanisms may be relevant to other inflammatory states.

We recently published an article showing that in the chronic renal failure setting, the rate of hypogonadism is of the order of 80%. So any diabetic dialysis patient is going to be by and large hypogonadal. These patients are currently being treated with erythropoietin, which, as you know, is an extremely expensive drug and is not without side effects. It is proinflammatory and increases the chance of vascular episodes. Be that as it may, we still need to treat anemia. In the article that we recently published in *Androgens* is the fact that testosterone administration can reduce the number of male patients getting erythropoietin by 50% or more in 3 to 6 months. Over a longer period of time, perhaps we will have even better results than that. So clearly another very important mechanistic appendage to our study to show the multidimensional actions of testosterone.

Dr. Morgentaler: Do you have a thought about the mechanism by which testosterone therapy can promote the risk of erythrocytosis?

Dr. Dandona: Yes. So probably what I have defined for you is the risk. To my mind, more than prostate-specific antigen, more than anything else, this is one risk we have. And I see, and I am sure you must have seen it, erythrocytosis occurs not infrequently.

Dr. Morgentaler: We see it routinely in our patients, particularly those on parenteral testosterone treatments such as injections and subcutaneous pellets.

Dr. Dandona: Unfortunately, there is no way of controlling it unless you take the patients off testosterone. And I find that to be a cruel thing to do because of the benefits that I have already described. So what I do is to send them to the Red Cross to donate blood. So it is kind of ready-made red cell factory ready to donate blood to those who need it.

Dr. Morgentaler: Please tell us about your recent study with testosterone therapy in diabetic patients.

Dr. Dandona: This retrospective study was conducted with Farid Saad and his group in Bremerhaven, Germany. It was in a group of hypogonadal type 2 diabetic patients who had been given testosterone supplementation for a period up to 11 years. The mean was 8 years. These patients were compared with hypogonadal men who did not get testosterone. What was interesting was that at 8 years, HbA1c levels in the testosterone group had improved in all hypogonadal patients given testosterone. The important thing to mention is that these patients were not being treated by other diabetologists. They were under their supervision and received standard diabetes treatment, but they were not interfering with their testosterone treatment. So, the effect was due to testosterone itself: 90% of the patients developed an A1c <7%, 80% of them got an A1c <6.5%, 50% got it <6.5% but some were still on treatment with antidiabetic drugs, but 33% were <6.5% without any treatment for diabetes at all. This was a testosterone effect, including the resolution of diabetes.

I wish we had a prospective study of this kind to demonstrate this reversal, because that would answer the question you posed to me right at the beginning when I said, "No, it is an interesting cycle." If you are obese and hypogonadal, you are insulin resistant and you get diabetes, but if you get testosterone, the whole thing reverses, so it is back and forth. I wish that we could actually propagate the use of testosterone over the long term in these patients, because not only is there a benefit in terms of sexual activity, but also there is a metabolic benefit, which is profound and improves the quality of life.

Dr. Morgentaler: Paresh, this has been wonderful. We have only a minute or so left. Would you like to make any final comments?

Dr. Dandona: So the final comment I would like to make is that we have such convincing data that testosterone improves insulin sensitivity, reduces adiposity, builds muscle, increases hematocrit, and so on, which we better get into the habit of measuring testosterone in every type 2 diabetic patient and every obese patient, because once we diagnose it, then as clinicians, we cannot resist treating. Once you have made a diagnosis, how would you find an excuse not to treat? And once you treat, you will see the amazing results of this treatment.

Dr. Morgentaler: Why do you think that other diabetes experts just are not aware, are they either not aware or whether they are resistant to the idea of testosterone?

Dr. Dandona: I think any new concept takes time to sink in. I think this is exactly what is happening. I mean, we are just 16 years from the first publication in 2004, and it can take a long time to change practice and habits. But really this is such a simple concept. As I said, mere measurement of testosterone concentrations can really change things for you because if you see a low testosterone in a patient, how would you resist giving testosterone to him? Now, given this sort of situation, I might just add an analogy here, that of menopause. The benefits of estradiol are phenomenal, and yet estradiol replacement has not taken off.

Dr. Morgentaler: In your own practice, what do you use to determine whether somebody is a candidate for testosterone therapy?

Dr. Dandona: A blood test is the start of the process and then the discussion with the patient regarding the implications of the results.

Dr. Morgentaler: And what do you use for a blood level for testosterone to make the diagnosis of testosterone deficiency?

Dr. Dandona: I go by the Endocrine Society guidelines, which had been 300 ng/dL, but I also invariably will measure free testosterone. That is a very important part because most type 2 diabetic patients and obese patients are insulin resistant, and we know that insulin-resistant states are associated with low SHBG, sex hormone binding globulin. So you can have a low testosterone total and yet when you measure or calculate free testosterone, it may be in the normal range because of the low SHBG. So, that becomes a very important part of the assessment of the patient.

Dr. Morgentaler: Paresh, is there any other novel area that you would like to speak about?

The other recent exciting development in our group has been the observation that most (~80%) morbidly obese adolescent boys have low total and free testosterone concentrations (TEEN LABS study). After bariatric surgery and weight loss for 2 years, their testosterone concentrations normalize. However, if these patients regain weight, their testosterone concentrations fall again. This is the best evidence that morbid obesity in boys may result in sexual impotence and possibly infertility and that after marked weight loss, these defects may reverse. Testosterone concentrations were inversely related to BMI in this study.

Paresh, it has been a total delight and extremely educational to speak with you. Thank you so much for sharing your experience.

Dr. Dandona: So kind of you Abe for inviting me to this. But as you can see, this area has become a major passion in my life.

Dr. Morgentaler: It is deserving of your considerable attention. Excellent. Thank you, Paresh.

Dr. Dandona: Thank you, Abe.

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Abbreviations Used

BMI = body mass index
ED = erectile dysfunction
FGF2 = fibroblast growth factor 2
FSH = follicle stimulating hormone
HIM = hypogonadism in males
LH = luteinizing hormone
SHBG = sex hormone binding globulin