DIABETES UPDATE

CB Sanjeevi*

ORAL INSULIN DELIVERY MAY SOON BE POSSIBLE

An oral insulin delivery system appears to have strong potential, according to researchers here at the 222nd National meeting of the American Chemical Society. The new delivery method, consisting of acrylic-based copolymers with a gel-like consistency, prevents metabolism of insulin until it reaches the small intestine. The delivery system has low reactivity in the low pH of the stomach, but has a higher swelling ratio in the higher pH of the small intestine. Lead investigator Aaron C. Foss of Purdue University, West Lafayette, Illinois, reported that the oral insulin delivery system has "worked beautifully" in laboratory experiments mimicking that environment. So far, effective methods of delivering insulin to the bloodstream in pill form have largely failed because the hormone is broken down as it passes through the stomach.

In an interview with Reuters Health, Purdue co-researcher Dr. Nicholas A. Peppas explained that the specially designed acrylic polymer mixed with insulin allows the hormone to successfully pass through the stomach largely unharmed, reaching the small intestine, where its polymer coating reacts with the intestinal environment to release "long chains that act as 'anchors,' "helping insulin adhere to the intestinal wall. The polymer helps create a "temporary opening of the tight junctions" between cells lining the small intestine, allowing passage of insulin into the bloodstream. In vitro studies and in studies conducted in rats and dogs, the polymer allowed about 16% of insulin to be delivered to the blood. This is a major advance over the 0.1% delivery rate of previous oral insulin delivery methods. Yet, improvements are needed before the technique can hope to rival the effectiveness of injections, Dr. Peppas cautioned. "Additional animal studies with larger animals will have to be done, followed by clinical studies. Meanwhile, we are also improving the formulation." According to a Purdue statement, the method, if successful, "could bring insulin pills and other products to market within a decade."

Reuters Health, Chicago, Aug. 27, 2001.

UPDATE ON ORAL (BOLUS) INSULIN

Preliminary results are showing oral insulin to be possibly more effective than subcutaneous insulin. Due to the fact, it is delivered directly to the portal circulation and then to the liver, which is consistent with normal physiology.

Emisphere Technologies, Inc. announced the results from phase three studies evaluating two of its proprietary drug delivery agents (carriers) for the oral delivery of insulin. The data, demonstrated absorption from the gastrointestinal tract with oral formulations of insulin, as well as significant reductions in blood glucose levels.

The first study, conducted by Hadassah Medical Center in Israel, consisted of the administration of insulin with an EMISPHERE(r) carrier in a capsule formulation to twelve healthy human volunteers who received one dose each, ranging from 200 to 405 units of insulin with carrier doses of 1.4 to 2.1g. The second study, conducted in The Netherlands, also consisted of insulin administration with the same EMISPHERE(r) carrier in a capsule formulation to six healthy human volunteers who received four different doses, ranging from 100 to 350 units of insulin and 1.4 to 2.1g of carrier, with another two subjects who received either the delivery agent alone at a dose of 2,100 mg or insulin alone at a dose of 350 units as a control. Emisphere also presented preliminary data from a third study that is being conducted in the U.K., and consists of oral insulin administration with an EMISPHERE(r) carrier that was selected and evaluated specifically for insulin, in 10 healthy human volunteers receiving three different doses, ranging from 100 to 150 units of insulin and 0.2 to 0.6g of carrier, and a subcutaneous control.

In all three studies, wherein one of Emisphere's proprietary carriers was used in combination with insulin in an oral formulation, Emisphere was able to demonstrate absorption from the gastrointestinal tract of clinically significant levels following oral dosing, with systemic concentrations reaching as high as 288µU/ml in one study. The data also demonstrated a rapid drop in blood sugar following oral insulin administration, with reductions up to 63% as well as a consistent compensatory decline in C-peptide levels. In addition, the orally delivered insulin had favorable pharmacokinetic and pharmacodynamic profiles, in that systemic blood insulin levels peaked at 25 minutes, and the maximum drop in blood glucose levels was seen 40 minutes after dosing. The studies demonstrated the safety and tolerability of both formulations.

** These abstracts are excerpted, with permission, from "The Diabetic News" edited by CB Sanjeevi.*

There were no serious adverse events or drug related side effects in any of the studies. The resulting preliminary data of the U.K.-conducted study suggested that the carrier specifically designed for insulin is the more effective of the two carriers tested.

Michael M. Goldberg, M.D., Chairman and Chief Executive Officer of Emisphere, stated, "We are extremely excited about the data from all three studies. Since insulin's discovery in 1921 there has been a concerted effort to develop an oral formulation. The results from these three studies met all of our expectations for the clear demonstration of the proof-of-concept. We are eager to partner this product with a suitable pharmaceutical company that can assist us in the rapid clinical development of a product that has the potential to significantly impact the lives of tens of millions of patients worldwide."

Alan C. Moses, M.D., Chief Medical Officer and Senior Vice President, Joslin Diabetes Center, stated, "The data are exciting on several levels. Besides demonstrating insulin absorption in the gastrointestinal tract, the studies were able to demonstrate a reduction in blood sugar levels appropriate for the serum insulin levels, a fast onset of action and a (dose-dependant) therapeutic response. The ability to deliver insulin into the liver before it reaches the systemic circulation is an important step in providing more physiological insulin delivery, something that investigators have been trying to do since the discovery and isolation of insulin. If oral insulin can be developed successfully, it will provide patients with diabetes a highly desirable option for insulin delivery that can be used early in type 2 diabetes and that can be used in combination with a single long-acting injection of insulin in type 1 diabetes."

Insulin represents Emisphere's second protein to enter human testing. Emisphere believes that an oral insulin product has the potential to benefit diabetics currently using subcutaneous insulin related to both patient compliance and physiological efficiency. Orally delivered insulin is expected to have distinct advantages over alternative delivery options, because it is delivered directly to the portal circulation and then to the liver, which is consistent with normal physiology.

Comment: The current studies have shown that if you could use the oral insulin as a bolus insulin with meals and if you add a basal insulin like Lantus, you could provide an excellent way to control blood sugars and prevent the complications of type 1 or 2 diabetes.

NON-INVASIVE BLOOD GLUCOSE MONITOR?

Being pricked in the finger hurts. What if you had to do it three times a day? For many diabetics, it is a painful regime that might eventually be eliminated thanks to a new device. Here's news about a medical breakthrough that is at diabetics' fingertips. There's a certain amount of discomfort involved in checking your finger sticks. And people are reluctant to check it as often as we like them to check it for that reason." That's why Dr. Sheehan, of the Joslin Diabetes Center at the University of Maryland in Baltimore, is excited about a new monitoring device, called the Diasensor 2000. "It uses near-infrared light transmitted through the skin to measure the glucose changes on a cellular level in a painless way," says Dr. Sheehan. The device is approved for use in Europe. Studies there have found that it measured blood sugar levels within 15 percent of traditional monitors. Its accuracy is now being studied at 10 centers in the United States. Diabetics testing the Diasensor 2000 still must monitor their sugar levels the traditional way. By comparing the readings done in finger tests, researchers can determine the accuracy of the new device.

The Diasensor was on display at the AADE convention in Louisville. Although it is very costly and too large to carry with you, continued research may make it smaller and less costly. Remember the first insulin pump? It had to be carried in a backpack!

ACOG ISSUES NEW GUIDELINES FOR MANAGEMENT OF GESTATIONAL DIABETES

The American College of Obstetricians and Gynecologists (ACOG) has issued new clinical guidelines to replace those issued in December 1994 regarding the management of gestational diabetes mellitus (GDM).

ACOG recommends in the September 2001, issue of Obstetrics and Gynecology that all pregnant patients be screened for GDM. In the absence of known risk factors for GDM, a personal history may be sufficient. However, the authors point out, many physicians choose to screen all pregnant patients. Dr. Coustan, who is affiliated with Brown University in Providence, Rhode Island, pointed out, "One problem is that there's not good solid evidence that screening a population is of benefit. Most believe it to be, but it's not malpractice not to."

The laboratory screening test should use a 50-gram, 1-hour glucose challenge at 24 to 28 weeks' gestation, with a threshold of 130 or 140 mg/dL. "In our bulletin we gave both sets of thresholds because either would be reasonable," Dr. Coustan said. "One of the problems is

that the relationship between glucose intolerance and macrosomia is probably not a step function, but a continuous function. So there's no one place above which you're absolutely abnormal, and no place below which you're guaranteed to be normal." Office-based glucose testing using capillary blood is generally not recommended.

The guidelines do not specifically recommend daily self-monitoring. However, if this is instituted, postprandial glucose values appear to be more informative than fasting levels in determining the likelihood of adverse pregnancy outcomes.

"This issue involves some controversy," Dr. Coustan said, "because people who have pre-existing diabetes usually monitor their preprandial glucose measurements outside of pregnancy. However, new data uncovered since the last issue of the bulletin caused us to change our view on postprandial glucose levels."

In its document, ACOG cautions that if the patient uses caloric restriction, the restriction should not exceed 33% of calories. Use of insulin should be considered if medical nutritional therapy fails. Failure would include fasting glucose levels >95 m/dL, 1-hour postprandial values greater than 130 to 140 mg/dL, or 2-hour postprandial values >120 mg/dL.

If the estimated fetal weight exceeds 4500 grams, cesarean delivery may reduce the likelihood of brachial plexus injury in the infant.

Obstet Gynecol 2001; 98: 525-538.

ELEVATED GLUCOSE INDUCES APOPTOSIS OF PANCREATIC BETA-CELLS

High levels of glucose appear to directly up regulate the cell death receptor Fas on human pancreatic beta-cells, according to Swiss and Israeli investigators. The finding may explain the loss of beta-cell mass seen in type 2 diabetes. Recognizing that human islets normally express the Fas ligand but not the Fas receptor, Dr. Marc Y. Donath, of the University Hospital in Zurich, Switzerland, incubated nondiabetic, cultured human islets in the presence of high concentrations of glucose. Fas receptor expression in the beta cells increased in a glucose dose-dependent manner. Glucose-exposed beta cells also exhibited a transient increase in proliferative capacity followed by a prolonged decrease, the investigators report in "Diabetes" for August 2001. At 1 day following exposure, post-mitotic apoptosis was evidenced by the presence of fragmented nuclei doublets. Anti-Fas antibody inhibited the deleterious effect of glucose, suggesting that the induction of apoptosis and impaired proliferation induced by glucose is caused by the interaction between constitutively expressed Fas ligand and upregulated Fas. Moreover, the researchers documented the presence of Fas receptor in islets of type 1 and type 2 diabetic patients, suggesting that a similar mechanism of beta-cell apoptosis underlies both diseases. "Our results underscore the importance of tight glucose control in limiting beta-cell destruction in all diabetic patients as well as in patients undergoing islet transplantation," Dr. Donath's team concludes.
Diabetes 2001, Aug.

PARASITIC WORMS TO PREVENT DIABETES AND LOSE WEIGHT?

PARASITES are good for you. British scientists have found that these unwelcome intestinal residents can provide protection against serious immune disorders. The discovery made by Cambridge researchers raises the prospect of making drugs that could block the development of such diseases. The group has already created a parasite extract, which could prevent animals from getting diabetes. Now they are working on a similar drug for humans. "We don't expect people to go around picking up parasite infections," said Professor Anne Cooke, of the university's pathology department. 'However, we hope to develop an extract that could trick the body into thinking it has been infested, thus setting off a reaction that prevents the onset of diabetes.'

The parasite-diabetes link was uncovered following work by Cooke's colleague, Dr David Dunne, who has studied parasite infection levels in Africa. Most people there show evidence of past or present infestations, particularly of schistosomiasis, the cause of the fatal illness bilharzia. By contrast, Dunne noted Africans suffer only low levels of autoimmune disorders. Such diseases - which include diabetes, multiple sclerosis and rheumatoid arthritis - occur when the bodies own defences attack its organs and tissue. For instance, diabetes is caused when a person's defence cells destroy the pancreas's insulin-secreting cells. "Essentially, in the West, the incidence of parasites in humans is low while the occurrence of auto-immune diseases - especially diabetes - is high and rising," said Dunne. "In other words, the position is the reverse of that in Africa." These contrasting patterns might have been dismissed as being a coincidence, were it not for the link uncovered by the Cambridge team. They and other groups have shown that special immune cells called TH1 cells usually trigger diabetes. By contrast,

parasite infections usually initiate a different group called TH2 cells. "The crucial point is that if you have high levels of one of these groups, say TH2, you tend to have low levels of the other, TH1. In other words, if you react to a parasite, you release lots of TH2, and this inhibits the amount of TH1 that your body makes. This in turn reduces the likelihood of you triggering an auto-immune disease," said Dunne.

In the developed nations, human parasites have largely been eradicated. Occasionally, cases of tapeworm in adults and pinworm in children are diagnosed but in general the West is free of such infestations. As a result, our bodies do not make so much TH2, and so its TH1 counterpart is not suppressed. The result has been rises in autoimmune diseases, say the Cambridge researchers. "This knowledge gives us a handle for controlling auto-immune disease by tricking the body into thinking it is under parasite attack, which is exactly what we did with the extract we isolated from schistosomiasis," said Cooke. "We gave it to a strain of mice that are genetically prone to develop diabetes. Each of them has an 80 per cent chance of contracting the disease. But when we injected them with the extract, none of them succumbed. It was amazingly effective."

The discovery has raised hopes that it may soon be possible to develop a similar drug for humans. 'We envisage that it would be given to people who are prone to diabetes, said Prof Cooke. 'However, as these extracts do not have any apparent side effects, it could simply be taken like a vitamin pill. "In addition, we are also testing to see if these extracts can prevent other auto-immune diseases such as rheumatoid arthritis. We are very hopeful." The Cambridge research effort has so far concentrated on developing parasite extracts to prevent autoimmune disorders, in particular diabetes. However, other researchers believe it may also be possible to counter allergies this way. Asthma, hay fever and other ailments have all risen just as human worm infestations in the developing world have declined, and they also display contrasting patterns of TH1-TH2 levels. This has led to hopes of developing similar drugs to limit the onset of allergies, and also triggered one worker, Prof Koichiro Fujita of Tokyo Medical and Dental University, to take the ultimate in hay fever cures. In a bid to stop his persistent seasonal sneezes, he now takes tapeworm eggs and currently hosts three of these unpleasant boarders. They have, he claims, cleared up his hay fever. Not surprisingly, they have also helped him to lose weight.

NEW COMPOUND MAY PREVENT, TREAT TYPE 1 DIABETES

A new compound has been found in marine sponges that could prevent type 1 diabetes, according to two reports published in the September issue of Nature Medicine. The compound, alpha-galactosylceramide (GalCer), binds to certain receptors on natural killer T cells (NKT cells) and stimulates the production of proteins that prevent the insulin-producing cells of the pancreas from being destroyed. NKT cells are part of the immune system and their numbers decline in people with type 1 diabetes, although it is not clear why, Dr. Terry L. Delovitch, senior author on one of the studies, told Reuters Health. But alpha-GalCer injected into non-obese diabetic mice prevented the mice from developing diabetes and prolonged the survival of islet cells that were transplanted into newly diabetic mice. The islet cells of the pancreas produce insulin. "These findings raise the possibility that alpha-GalCer treatment might be used therapeutically to prevent the onset and recurrence of human type 1 diabetes," Delovitch, of the University of Western Ontario, Canada, and an international team of scientists conclude in their report. The researchers said that the compound has been deemed safe in preliminary studies of patients with colorectal cancer. But further research is needed to show that alpha-GalCer is effective in humans before the compound is given to patients with type 1 diabetes.

In the second study, researchers garnered similar results when they gave alpha-GalCer to mice that were genetically predisposed to develop diabetes. Left untreated, about 90% of the mice should have developed type 1 diabetes. But only 10% to 20% of mice treated with alpha-GalCer developed the disease, according to the results. What this means is that you would need to start treatment before severe symptoms of diabetes have developed and individuals that are at (genetic) risk for developing diabetes could be treated.

Alpha-GalCer was originally isolated by a Japanese company that is currently conducting clinical studies on the treatment of cancer in humans. Type 1 diabetes is a disease in which the body's immune system attacks the insulin-producing cells of the pancreas. Insulin is the hormone that deposits glucose (sugar) from the blood into cells throughout the body to use as energy. People with type 1 diabetes rely on daily insulin injections to control their blood sugar.

Nature Medicine 2001; 7:1052-1062.

PROMISING NEW TREATMENT FOR EARLY TYPE 2 DIABETES

A new treatment paradigm for early type 2 diabetes, described in the May issue of *Diabetes Care*, involves inhibition of dipeptidyl peptidase IV (DPP IV).

"This study provides the first evidence that pharmacological DPP IV inhibition is feasible for the treatment of type 2 diabetes in humans", "write Bo Ahren, MD, from Lund University in Malmo, Sweden, and colleagues.

Although glucagon-like peptide-1 (GLP-1) has potential for treatment of type 2 diabetes, its short half-life prompted investigation of inhibitors of the GLP-1-degrading enzyme DPP IV, which improve glucose tolerance in insulin-resistant rats and mice.

This double-blind, multicenter trial involved the selective, orally active DPP IV inhibitor NVP DPP 728. Over the 4-week treatment period, 61 men and 32 women with diet-controlled type 2 diabetes (mean age, 64 years) received placebo or the inhibitor at a dose of 100 mg three times daily or 150 mg twice daily. There were no significant adverse effects.

Compared with placebo, NVP DPP728 at 100 mg three times daily reduced mean fasting glucose by 1.0 mmol/L, prandial glucose excursions by 1.2 mmol/L, and mean 24-hour glucose levels by 1.0 mmol/l (all $P<.001$). Reductions were similar in subjects receiving 150 mg twice daily, and mean 24-hour insulin levels were reduced by 26 pmol/L in both active treatment groups. An unexpected benefit was that HbA_{1c} in the combined active treatment groups decreased by 0.6% ($P<.001$).

"There was no difference between a three-times-daily treatment schedule versus a twice-daily treatment schedule with NVP DPP728, indicating that either dosing regimen could probably be used with equal efficacy", the authors write. "Further long-term studies will be needed to examine the long-term effects of DPP IV inhibition as well as to fully understand the mechanism of the effects and to define the use of this approach in patients with more advanced diabetes and in combination with other antidiabetic drugs."
Diabetes Care. 2002; 25(5):869-875

TRIAL OF ARTFICIAL PANCREAS SET FOR LAUNCH

Clinical trials will begin next month for a prototype artificial pancreas that should enable patients with type 1 diabetes to have more controlled levels of blood glucose with fewer episodes of hypoglycemia than are achievable with insulin pumps, say scientists at City University here.

"Our prototype artificial pancreas administers continuous subcutaneous insulin that maintains glucose at a constant level. It has the potential to reduce the most dangerous aspects of diabetes such as hypoglycemia, amputations and blindness," said Dr. Roman Hovorka, the researcher heading the study from City University.

The prototype is made up of three parts: a sensor placed on the skin takes a blood sample to measure glucose levels; a hand-held computer analyses the information using a control algorithm; a small pump infuses glucose into the body.

It will be small enough for men to fit it on their belts or women to place it inside their bras," said Dr. Hovorka. He hopes the product will be on the market in five years.

Funded by the European Commission and insulin pump manufacturer Dietronic, the project is believed to be at a further stage than similar versions in the US. Dr. Hovorka said that US competitors have still not begun clinical trials.

The first randomized, controlled trial for the prototype takes place next month in a hospital in Austria. Twelve subjects will be maintained in the hospital for 24 hours on two occasions. They will first be given treatment via insulin pumps currently used in Europe, and will then use the artifical pancreas.

Since January 2000, Dr. Hovorka has tested the prototype on over 20 volunteers in Austria and Italy, achieving "very promising results." Their glucose levels were maintained at an average of 6.2 mmol/L (125mg/dL). The normal is about 5.5 mmol/L (111 mg/dL) and most insulin-dependent diabetics can only maintain an average of 8.9 mmol/L (179 mg/dL) using the methods currently available, he noted.

A unique computer model of the disease, on display at City University on Friday, has also aided research. Nicknamed Bina, the computer holds data of a number of diabetic profiles. The scientists were able to test various components of the prototype without the need for animal testing using the computer model.

"We believe this product will have a significant and important effect on the lives of people with type 1 diabetes. But the technology is expensive, so we will not be able to help everyone," added Dr. Hovorka.

Source : Reuters News, May 09, London.

GLYCEMIC INDEX HELPFUL IN FOOD SELECTION

A systematic review of studies using the glycemic index to classify foods suggests that the approach can help select foods that decrease risk of obesity, type 2 diabetes, and heart disease. Another article describes improvements in total fat mass and lipid profile in healthy, overweight men on a 5-week low -glycemic index diet.

"The rate of carbohyydrate absorption after a meal, as quantified by glycemic index, has significant effects on postprandial hormonal and metabolic responses," writes David S. Ludwig, MD, PhD, from Children's Hospital in Boston. "Despite areas of continuing controversy, clinical use of glycemic index as a qualitative guide to food selection would seem to be prudent in view of the preponderance of evidence suggesting benefit and absence of adverse effects."

Ludwig recommends increased consumption of fruits, vegetables, legumes, and grains processed by traditional rather than modern methods, and limited intake of potatoes and concentrated sugar.

In the separate study from INSERM in Paris and Lyon, France, 11 healthy men were randomly allocated to 5 weeks of a low- or high-glycemic index (LGI or HGI) diet separated by a 5-week washout period in a crossover design. Compared with the HGI diet, the LGI diet resulted in lower postprandial plasma glucose and insulin profiles and areas under the curve, lower plasma triacylglycerol excursion after lunch, decreased total fat mass by approximately 700 g, and a tendency to increase lean body mass without changing body weight. Decreased leptin, lipoprotein lipase, and hormone-sensitive lipase mRNA quantities in the subcutaneous abdominal adipose tissue accompanied decreased fat mass.

"Five weeks of an LGI diet ameliorates some plasma lipid parameters, decreases total fat mass, and tends to increase lean body mass without changing body weight," write Clara Bouche, MD, and colleagues. "These changes were accompanied by a decrease in the expression of some genes implicated in lipid metabolism. Such a diet could be of benefit to healthy, slightly overweight subjects and might play a role in the prevention of metabolic diseases and their cardiovascular complications."

JAMA. 2002;287(18):2414-23 and Diabetes Care. 2002;25(5):822-8

METFORMIN GLUCOSE TOLERANCE IN TEENS WITH POLYCYSTIC OVARY SYNDROME

Adolescents with polycystic ovary syndrome (PCOS), obesity, and impaired glucose tolerance benefit from therapy with metformin, according to an open-label trial conducted at Children's Hospital of Pittsburgh.

Dr. Silva A. Arslanian and associates treated 15 girls with metformin hydrochloride initiated at 850 mg/day. After 1 to 2 weeks, the dose was increased to 850 mg b.i.d.

Body mass index (BMI) decreased significantly after 3 months, from a mean of 38.1 to 36.7. Oral glucose tolerance improved significantly, with 2-hour glucose values dropping from 9.1 to 7.4 mmol/L. Eight girls achieved normal glucose tolerance. Hepatic and peripheral insulin resistance and fasting insulinemia also improved.

Six subjects experienced greater menstrual cyclicity, and adrenal hyper-responsiveness to adrenal corticotrophic hormone was attenuated. An observed correlation between insulin levels and ACTH stimulatory responses "do not imply causation, but may be suggestive of a role for insulin in adrenal hyperandrogenism", Dr. Arslanian's group maintains.

J Clin Endorcrinol Metab 2002, 87:1555-9.

DIABETES DRUG ROSIGLITAZONE RESULTS IN MINIMAL HEPATOTOXICITY

Type 2 diabetes drug rosiglitazone (Avandia) does not appear to cause any more harm to the liver than other types of diabetes drugs, such as insulin, according to a new report.

And unlike a related compound, troglitazone (Rezulin), rosiglitazone is not associated with liver failure, according to a report published in the May issue of the journal Diabetes Care.

Rezulin was taken off the market two years ago because of concerns about possible liver damage. This sparked concern about the possibility of the other glitazone drugs causing similar liver damage or liver failure.

A review of clinical trials originally conducted by Smith Kline Beecham Pharmaceuticals, the maker of

Avandia, was undertaken by Dr. Harold E. Lebovitz of State University of New York in Brooklyn.

For the review, Dr. Lebovitz and his team re-examined the data from 13 studies that originally aimed to examine the efficacy and safety of Avandia.

"No evidence of [hepatotoxicity] was observed in studies that involved 5006 patients taking rosiglitazone," Dr. Lebovitz and colleagues write.

"The study is reassuring in that they did not find significant increases in liver damage from [rosiglitazone] compared to any of the other classes of diabetes drugs," said Dr. Christopher Saudek, president of the American Diabetes Association, in an interview with Reuters Health.

Diabetes Care 2002;25:815-21.

WHO GETS AGGRESSIVE ON OBESITY

Obesity has reached such epidemic proportions that world health officials have decided they need to take a more aggressive approach if they are to head off a global explosion of fat-related diseases.

After years of focusing on promoting healthy eating to dampen demand for junk food, the World Health Organization is now examining what can be done on the supply side, enlisting the cooperation of food producers.

In the last two years, experts have confirmed that obesity, diabetes and heart disease, commonly thought to be afflictions of the affluent, are spreading to the developing world, but new research provides the clearest picture yet of the global situation.

Studies presented at the annual meeting of the WHO's decision making body provide the first major insight into childhood obesity rates in the developing world.

The picture looks all too familiar, even in regions suffering from malnutrition. Figures from Africa, the Middle East, Latin America and the Caribbean were included.

"We estimate that 22 million of the world's children under five years are overweight or obese," said Mary Bellizzi, an expert with the International Obesity Task Force who presented the research to health ministers at the meeting.

Research indicates that in some parts of Africa, fatness and obesity afflicts more children than malnutrition does; sometimes four times as many.

"In small studies in Africa you will find that 0.7 percent of the children are showing features of malnutrition, but over 3 percent are showing up overweight or obese," said Neville Rigby, public affairs director at the International Obesity Task Force.

The organization estimates that 300 million people worldwide are obese and 750 million more are overweight. In the United States, some 60 percent of adults are overweight or obese, as are nearly 13 percent of children. The obesity task force estimates that in some countries, more than 30 percent of the children are obese. Bellizzi reported that in Egypt more than 25 percent of four year-olds are fat and that obesity rates are also more than 25 percent among children aged between 4 and 10 in Chile, Peru and Mexico. In Zambia and Morocco, between 15 and 20 percent of four-year-olds are obese.

"I think it's time to do something serious," Bellizzi said, after the meeting. "Education is not enough."

"You have to look at food production, food importation - the production of sugar, the production of oil, that has to go into food and that food is ultimately sold to consumers," she said.

"If we continue with this production, that produce has to go somewhere and people have to eat it, so I think we need to have a radical look at food supply in order to make sure that food that is supplied to the public is lower in fat, sugar and salt," Bellizzi said.

WHO experts are starting to do just that. "Our general view is that guilting people, in the long run, doesn't work," said Dr. Derek Yach, WHO executive director for noncommunicable diseases and mental health.

"There are two strategies. One is working at the level of individuals, to give them the best information so that they can make informed choices," he said. "Step two often requires removing some of the heavy handed marketing that may block them making those choices in an informed way, particularly at a young age."

Although WHO believes junk food consumption has to be controlled, it is not approaching the issue as aggressively as it has tackled tobacco. WHO has a combative relationship with the tobacco industry and is crafting international legislation to seriously curtail tobacco consumption. "We think that before we enter into policy decisions about food, we have very serious discussions to have with the food industry," Yach said.

"We believe there is an enormous potential to work together to solve these problems, whereas we didn't believe that in the case of the tobacco industry. "Our preliminary discussions with the food industry indicate a great willingness to talk to us," he said.

"It may very well be that they will look at advertising, but we are interested in what they will do positively with us - promoting physical activity on a worldwide scale, trying to make the less salty, less sugary, less fatty products more available and more attractive to young people."

Emma Ross, Associated Press

SEXUAL PROBLEMS COMMON IN DIABETIC WOMEN

Women with type 1 diabetes frequently experience sexual dysfunction, according to a report in the April issue of Diabetes Care.

Dr. Koen Demyttenaere, of University Hospitals Gasthuisberg, Leuven, Belgium and colleagues asked 120 women with type 1 diabetes and 180 age-matched healthy controls to answer questionaires on sexual function, marital satisfaction, and depression. The diabetic women were also asked about psychological adjustment to diabetes.

The researchers obtained data on HbA_{1c}, use of medication, body mass index, and early onset microvascular complications from medical records.

Ninety-seven women in the diabetic group and 145 in the control group completed the questionaires. Sexual dysfunction was reported by 27% and 15% of the diabetic and control women, respectively (p+00.04), "but a significant difference was found only for decreased lubrication."

"No association was found between sexual dysfunction and age, body mass index, duration of diabetes, HbA_{1c}, use of medication, menopausal status, or complications," the team writes.

They note that the more diabetes complications a woman had, the more sexual dysfunctions she experienced (p=0.002). They add that treatment satisfaction was altered by the presence of complications.

Women in both groups who reported sexual dysfunction had overall lower quality of marital satisfaction ($p < 0.001$) and more symptoms of depression ($p < 0.001$) than those without sexual dysfunction. Depression significantly predicted sexual dysfunction in both groups of women.

The findings "suggest that psychological and not diabetes-related somatic factors are related to sexual dysfunction in women with diabetes, "Dr. Demyttenaere and colleagues conclude. "The sexual problems of women with diabetes deserve more attention in clinical research and practice."

Diabetes Care 2002;25:672-7.

LOW ADIPONECTIN LEVEL LINKED TO INSULIN RESISTANCE AND BMI IN TEENS

The adipose-derived cytokine adiponectin could be useful in predicting an increased risk of type 2 diabetes in children, according to preliminary research findings presented here at the annual Experimental Biology 2002 conference in New Orleans.

According to Dr. Dan Nemet, with the University of California at Irvine, adipose-derived cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and adiponectin, may contribute to worsening insulin resistance in the growing child, as has been found previously in adults.

To test whether these cytokines might serve as markers for impaired insulin sensitivity, Dr. Nemet and colleagues measured levels of TNF-α, IL-6 and adiponectin in a predominately lower socioeconomic group of Hispanic-American children. The subjects included 17 boys and 14 girls, with an average age of 13 years. Their weight ranged from below normal to severely obese.

Adiponectin levels were inversely correlated with body mass index (BMI) and percent body fat, as measured by dual-energy X-ray absorptiometry (DEXA) and skinfold test. In contrast, TNF-α was positively correlated with BMI and skinfold test; and IL-6 was positively correlated with BMI and DEXA.

Fasting insulin was inversely correlated with adiponectin, but not with TNF-α or IL-6, the researchers found.

The data suggest that "the development of type 2 diabetes in children may involve dysregulation of adiponectin secretion," the authors conclude.

Emma Hit. Reuters, Apr. 24, New Orleans.