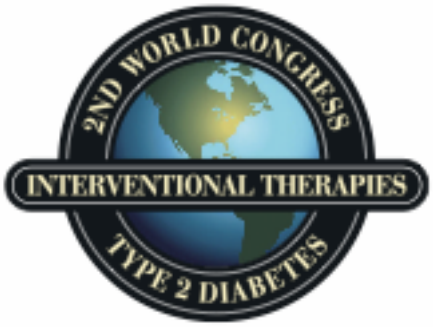

NOTES FROM THE CONGRESS

The2nd World Congress on Interventional Therapies for Type 2 Diabetes (WCIDT) held in New York on March 28-30, 2011 was co-organized by the *Weill Cornell Medical College* (*New York*), the *New York Presbyterian Hospital*, and *the Giovanni Lorenzini Medical Science Foundation (Milan, Houston)*. The 2nd WCIDT was third in a series of educational events to increase and enhance knowledge on the use of metabolic surgery in obese diabetic patients. The first was the *Diabetes Surgery Summit* held in Rome in 2007 followed by the *1st WCIDT* held in 2008 in New York. This most recent Congress was designed for professionals in the fields of endocrinology, diabetes, bariatric/metabolic surgery, cardiology, epidemiology, gastroenterology, internal medicine, family medicine, pharmacology, nutrition, basic science, and public health, as well as allied health professionals, policy makers, and scientists from the pharmaceutical and medical device industries.

The comprehensive, multidisciplinary forum was led by a largely representative group of international experts who conducted a critical review and discussion on the latest research findings on metabolic/bariatric surgery and novel interventional therapies for type 2 diabetes. More than 60 countries were represented by 75 faculty (including two Nobel Laureates), 32 Guest Experts, and some 1,000 participants. In more than 25 hours of activity, participants were able to have deep, comprehensive, and unbiased discussions on a panorama of clinical, research, and policy issues related to the ongoing studies on the use of gastrointestinal interventions, resulting in an improvement in the understanding of diabetes. One major objective of these discussions and interactions among members of the faculty and audience was to provide direction for future treatments of curative intent.
At the end of each session, multidisciplinary panels held open-minded discussions which highlighted both the agreements and disagreements on the presentations made during the individual sessions. Three breakout sessions offered all participants the opportunity to democratically participate in defining the next steps.

Day 1: Clinical Issues

In his introduction *Francesco Rubino* outlined the scope of the meeting: a) new findings b) controversies; c) appropriate candidates for surgical treatment of diabetes; d) proposed policy changes to facilitate access to surgery for eligible patients, e) conventional paradigms and new hypotheses.
The overarching aim of the Congress was to understand and discuss the many open questions that the bariatric surgery poses— not just as the established treatment of morbid obesity but also as a new approach to the treatment of diabetes.

In the initial presentations, ***glycemic and metabolic control*** with current pharmacologic treatment (*Stefano Del Prato*) was compared with glycemic and metabolic outcomes of bariatric/metabolic surgery *(Philip Shauer).* Pharmaceutical control can provide strict and long-term glycemic control; it does not ensure clear cut benefits in terms of long-term complications, unless proper therapy is initiated early in the course of the disease; and early intervention can be more effective, though not necessarily simpler. On the other hand, bariatric/metabolic surgery is effective in morbidly obese patients with type 2 diabetes (T2DM); in the treated patients weight loss is sustained up to 4 years and glucose metabolism and glycemic control (HbA1c) are improved significantly; and there is strong evidence and consensus for bariatric surgery as a treatment for T2DM, especially for obese patients not well controlled with medications.

The ***safety profiles*** of both pharmaceutical (*Harold Lebovitz*) and surgical (*Bruce Wolfe*) approaches were compared. On the pharmaceutical side issues that should be taken in consideration are: benefits must be clinically significant in the majority of treated patients; the risk/benefit ratio should be taken in consideration; and possible side effects should be reversible. Safety issues with regard to surgery should consider the type of procedure, the value of BMI, the inability to walk, the history of venous thrombosis/pulmonary embolism, and the history of obstructive sleep apnea. Indicators could be the percentage of hospitalizations before and after the operation. Suicide does not appear to be linked to bariatric surgery.

Questions and controversies to be debated: Is the definition of metabolic surgery, or diabetes surgery, or interventional diabetology a philosophical or semantic issue? Is the target the obese subject with metabolic disorders or the obese with diabetes or the diabetes patient? Other questions: who should be responsible of the selection of patients, who should address the patients to the surgeons and to assure the follow-up?
The pathway of the patients should take in consideration (*Francesco Rubino*): indication; preoperative diagnostic evaluation; defining characteristics/stage of diseases; choice of procedure; definition of treatment success; assessment of postoperative outcomes; type of follow-up; complementary therapies; and definition of “care team”.

Guidelines for the surgical treatment of obesity and diabetes (*Lee Kaplan*) are based on the NIH 1991 consensus that focused on obesity, not diabetes. They included diet, exercise, and only then gastric reduction with bypass only in front of a well motivated patient. In 2007 diabetes was

included as part of the guidelines in that surgery should be considered for treatment of T2DM as an alternative treatment in inadequately controlled T2DM in patients with BMI 30-35 kg/m^2. Randomized controlled trials (RCT) were strongly encouraged to assess the utility of GI surgery to treat T2DM. In patients with BMI < 35 kg/m^2, determination of the appropriate use of GI surgery became an important research priority. In the ADA Guidelines of 2009, bariatric surgery was to be considered for adults with BMI > 35 kg/m^2 and type 2 diabetes, especially if the diabetes or associated co-morbidities were difficult to control with lifestyle and pharmacological therapy. After bariatric surgery patients need lifelong lifestyle support and medical monitoring. There is currently insufficient evidence to generally recommend surgery in patients with BMI < 35 kg/m^2 outside of a research protocol. The long-term benefits, cost-effectiveness and risks of bariatric surgery in individuals with type 2 diabetes should be studied in well-designed, randomized controlled trials versus optimal medical and lifestyle therapy. The Institute for Clinical Systems Improvement (2010) recently discussed bariatric surgery as an option for some individuals with type 2 diabetes and a BMI of 35 kg/m^2 or more. Bariatric surgery can result in marked improvements in glycemia; however, the long-term benefits and risks need to be studied further.

The ***worldwide epidemic*** of increasing of type 2 diabetes (*Paul Zimmet)* calls for strategies to prioritise severely obese persons with type 2 diabetes to ensure that bariatric interventions are available to those that most likely can receive benefit. Obesity and type 2 diabetes are chronic diseases with complex metabolic disorders that increase the risk of CVD and death.
http://www.healtheurope.org/index.php?option=com_content&task=view&id=185&Itemid=0
Tackling "Diabesity" on a global scale must be a goal. Other goals include: development of practical recommendations for clinicians regarding patient selection and management, identification of barriers to surgical access, creation of health policies that ensure equitable access to surgery, and identification of research priorities. The *International Diabetes Federation (IDF) Position Statement* notes:
"Bariatric surgery is an appropriate treatment for people with type 2 diabetes and obesity not achieving recommended treatment targets with medical therapies, especially when there are other major co-morbidities. Surgery should be an accepted option in people who have type 2 diabetes and BMI of 35 or more. Surgery should also be considered as an alternative treatment option in persons with BMI 30 to 35 when diabetes cannot be adequately controlled by optimal medical regimen, especially in the presence of other major cardiovascular disease risk factors. In Asian, and some other ethnicities of increased risk, BMI action points may be lower e.g. BMI 27.5 to 32.5" (see the full statement as attached).

Medical versus surgical procedures were compared in the Clinical Track session II. The impact of pharmacologic approaches on diabetes-related CV risk, CVD mortality (*Robert Eckel)* was once again compared with the long-term impact of bariatric surgery on CV risk and CVD *(Lars Sjöström* and *Ted Adams)*. What are the risk factors for CVD in patients with T2DM? Hypertension: current guidelines seem correct. Dyslipidemia: current guidelines seem correct. Glycemia: HbA_{1c} < 7.0%. Inflammation: reduce weight and treat other CVD risk. Thrombosis: aspirin for secondary prevention only.

Other questions?

- *What are the predictive factors for diabetes control for patients considering surgery?*

Duration of T2DM, insulin use, and HbA1c, represent predictors of glycemic control (*Judith Korner*); age and C-peptide could be added. However pre-op BMI does not predict outcome when

starting with a BMI > 35. Gender and race/ethnicity deserve detailed analyses; less information is available on waist circumference.

- *Are there options for pre-op management of bariatric surgery patients with T2DM?*

Weight loss and glycemic control and control of other co-morbidities are options in pre-op management (*Caroline Apovian*). HbA1c reduction means reduction of vascular problems. Good prognostic indicators for eradication of diabetes are duration of diabetes, diet/lifestyle-controlled diabetes, presence of T2DM over T1DM, and significant weight loss after surgery.

- *Which surgical procedure is best?*

A summary of available evidence from comparative clinical studies in high and low BMI patients was presented (*Harvey Sugerman*). More randomized clinical trials among the different procedures are required to better identify long-term outcomes of micro- and macro-vascular diseases: renal failure, amputation, retinopathy, etc.

- *What about post-operative management of obese and diabetic patients?*

An integrated multimodality therapies approach is requested in the postoperative management of obese and diabetic patients (*Louis Aronne*). A combined surgical and optimized medical therapy and "weight-centric" management of the post-operative patient should produce the best results. The new specialty "Obesity Medicine" will complete the concept of a surgical center of excellence.

- *What about the rational and physiological approach to the management of diabetes after bariatric surgery*?

Ralph De Fronzo started with three main assumptions: a) patients become "non-diabetic" within days after surgery, before significant weight loss has occurred; b)weight loss, secondary to caloric restriction and gastric banding, does not produce similar rates of diabetes reversal; c) diabetes resolved within one week after Roux-en-Y gastric bypass (RYGB), but not after gastric banding. In the ≥ 80% of T2DM subjects submitted to RYGB, the diabetes resolves and no further therapy is required. In the 20% of T2DM whose diabetes does not resolve after RYGB, Glucagon-like peptide-1 (GLP-1) receptor agonists or insulin sensitizers (metformin and pioglitazone) should be considered.

Day 2: Research Issues

- *What other mechanisms produced weight loss beyond restriction and malabsorption?*

Surgical outcomes beyond weight loss (*Randy J. Seeley)* are improvement in metabolic diseases and the effects on physiological processes that influence metabolism. After surgery animals eat less and modify quality of food with reduced fat and calories.

- *What about the effect of GI surgery on insulin secretion and sensitivity?*

Metabolic changes *(Samuel Klein*) produced by bariatric surgery, shown by evaluation of HOM-IR for insulin secretion and HOMA-beta, are independent from weight loss. GLP-1 increase insulin secretion and it is independent from weight loss. RYGB does not have weight loss-independent effects on skeletal muscle insulin sensitivity (the effect on liver insulin sensitivity is not known).

- *What is the effect of surgery on food choice?*

Studies on metabolic efficacy and changes in taste through evaluation of post-surgery response, using metabolic chamber, diet-induced thermogenesis, and assessment of food preference in rats with sham or bypass, help to better understand weight loss and gain, food intake, and energy expenditure *(Carel Le Roux).* The concept of reward and the evaluation of taste domain, are

explained by the pyramid: physiology (pick), reward (medium), how much do like it, hedonism discrimination sensory (basis).how is it ("what is it?").

- *Is glucose homeostasis after surgery dependent on weight loss or not*?

Dramatic improvement in glucose metabolism *(Jens Holst*) within days after surgery and with only minor weight loss may be seen. Improved insulin sensitivity may be a result of hypocaloric diet. Improved beta cell function may be the consequence of gastrointestinal factors. In the first days after surgery a 50 % reduction in insulin resistance is observed because of negative energy balance (fasting). The rapid transit of chyme from the esophagus to the ileum with high density of L-cells obtains increased GLP-1 responses to meals with an ensuing stimulation of insulin secretion.

A *debate* between *David Cummings and Ele Ferrannini* about *the weight independency of diabetes control after GI surgery*

Yes, says *David Cummings:* after RYGB insulin sensitivity is increased in liver hepatic, muscle, and adipose tissue and inflammatory cytokines decreased. The longer-term effect shows increased GLP-1 and decreased ghrelin. The increase of insulin sensitivity (COSMID trial) produces an 88% remission in diabetes, 11% improvement, and 1% no effect.

No, says *Ele Ferrannini*: in morbidly obese patients undergoing RYGB, liver, adipose tissue, and muscle insulin sensitivity and the pattern of substrate utilization are improved at one-year post-surgery in proportion to the weight loss; soon after surgery, the changes in plasma glucose and insulin levels and hepatic glucose production can be explained by caloric restriction; and diabetes remission is dependent on the starting degree of impairment of ß-cell function.

Further questions on novel experimental approaches for diabetes/obesity

- *Why address low BMI patients? What's the background for novel procedures? Do lower BMIs need massive weight loss? Do low BMI patients, with mild insulin resistance need the pylorus to gain better glycemic/metabolic control? Is there any physiological importance for preserving the pylorus?*

Many of these questions were answered by *Ricardo Cohen.* Delaying gastric emptying proved to be an efficient means of reducing postprandial glucose excursions in diabetics and healthy subjects secondary to incretin effect. Preserving the pylorus may be important to diabetes mellitus (DM) control after GI surgery.

- *Are endoluminal procedures for obesity/diabetes coping with the expectations of bariatric surgeons*?

Endoluminal therapy for obesity/metabolic disease is still in the early stages (*Stacy Brethauer*). It appears to be safe.

- *What is the efficiency of endoluminal devices for obesity/diabetes?*

Gastric bypass, BPD/DS, endoluminal sleeve, ileal interposition, gastric banding, and gastric plication were compared in terms of impact on weight, food intake, energy expenditure, and glucose metabolism *(Lee Kaplan).* Intragastric balloons, gastric and intestinal approaches are under evaluation.

Endoluminal duodenal-jejunal sleeve (ELS) induces weight loss in human subjects, improves diabetes in human subjects, improves obesity and diabetes, improves insulin sensitivity, increases postprandial GLP-1, induces increased energy expenditure.

- *What about pacing/GI electric stimulation for diabetes?*

Harold Lebovitz describes the pros and cons of *Tantalus* that sends a signal through vagus to CNS centers regulating glucose, insulin, glucagon levels, satiety, and blood pressure similar to those activated by GLP-1. Neuronal signalings decrease of HBA1c by 1%, decrease blood pressure. Comparison between *tantalus* treatment and GLP-1 related treatments. *Tantalus* has no effect on GLP-1, but also no nausea and no vomiting.

Questions on priorities for clinical research in metabolic/diabetes surgery focus attention on ongoing trials; challenges for study design; practical issues in surgical trials

- *The question is how to compare medical and bariatric surgical therapies in risk/benefit profiles over the short and long term?*

There are multiple small ongoing trials with a total of more than 1,300 subjects (*Allison Goldfine*). All trials are < 5 years of observation. Developing a team approach, with an integrated database and longer duration follow-up is a high priority. There is uncertainty regarding how improvements from bariatric surgical approaches align with those of medical diabetes and weight management. Selection of the endpoint, recruitment, duration/retention cost will impact greatly on the trial design.

- *Is the existing evidence sufficient?*

There are too many examples of exceedingly eager surgeons, wanting to help but doing the opposite. There is an overwhelming amount of evidence of poor quality (*Bjørn Hofmann)*. As in other kinds of surgery there is an imperative to do research, and there is an imperative to do good research. Etiology is complex and not well established. Intervention mechanisms are not well known. BMI is not adequate. Selecting inclusion criteria is both a scientific and a moral issue.

- *What about the advantages/disadvantages of study designs?*

Francesco Rubino compared multi-site versus the consortium model for large clinical trials. Critical issues are: limited evidence-based data; lack of well-controlled long-term studies; lack of randomized clinical trials comparing surgical procedures head to head. Additional issues are surgeons' egos; dogmatism; lack of academic interest difficult to randomize; learning curve; costs of treatment; costs of complications.

- *Who pays for them? What questions need to be addressed by Randomized Clinical Trials?*

Needs of RCTs for subjects < 35 BMI; costs and funding are limiting research. There is a need for hard comparisons of surgical procedures. Criteria for participation in the consortium were discussed. There is a need of the involvement of a multi-disciplinary team including at least one surgeon, one diabetes specialist (endocrinologist/diabetologist) and one nutritionist/dietician as co-investigators.

Questions on policy issues

The global epidemiology of diabetes *(Paul Zimmet)* represents the World Diabetes Perfect Storm: in 2010 diabetic subjects are 285 million; in 2030 they will become 438 million, an increase of 54%. The alarm is worse in Africa and Asia. China now has 90 million people with diabetes. In 2006 there was a resolution by the UN General Assembly to support policy interventions to block the diabetes pandemic. One critical issue is epigenetics: how we eat and live can change the way our genes behave starting with the maternal environment.

- *What about the global costs of diabetes?*

In the US: 116 billion in 2007, 10% of total health expenditures (*Linong Ji*). In China 17.9 billion in 2008 9.4% of total health expenditures. Pro-capita costs are more than USD ? 6,500 $ in the US and Norway; $ 3,000 in Australia, UK, Canada, Finland, Sweden, Germany and France. $1,500 in Spain and *Prevention and treatment strategies may help reduce costs*

- *Is bariatric surgery a cost-effective intervention for managing type 2 diabetes in the obese population?*

Cost-effectiveness is the issue **(***Catherine Keating*). The literature-based study reported costs per QALY ranging from $ 7,000 to 11,000 depending on the bariatric surgery type. The effectiveness threshold/ interpretation in the US is 55,000 $ /year. QALY cost for BMI > 40 is 2,800 £ in UK; 7.000 US$ in the US. For BMI 30-40 the costs are 1,360 £ in UK; 12,000 US$ in US. More knowledge is requested on the cost-effectiveness of bariatric surgery as a therapy for type 2 diabetes in those with a BMI < 35. Knowledge is uncertain on which bariatric surgery procedure is the most cost-effective therapy for managing obese patients with type 2 diabetes. Bariatric surgery potentially saves healthcare costs and generates health benefits in some patients, particularly where recent-onset diabetes is targeted in best practice clinical settings. Bariatric surgery is up to twice as cost-effective in the obese sub-population with diabetes than in the general severely obese population. Conclusions are robust that bariatric surgery is "very cost-effective" in the USA, UK, European, and Australian set for managing type 2 diabetes in the obese (BMI > 35).

- *What about return of investment?*

Bariatric surgery does not significantly reduce costs, but it avoids rising costs that continue to occur.

- *How should governments consider evidence on cost-effectiveness?*

The goal is to reduce uncertainty/variation around appropriate use of Health Technology Assessment (HTA) – an approach to evaluating medical technology *(Sean Sullivan)*.

The paradox of innovation technology is rapid proliferation of payers, and response by policy makers, but randomized trials are not sufficient. Reference price and price volume should be agreed upon. Until additional evidence is generated coverage could be denied. *No cure, no pay?* If the treatment does not cure, relieve, or prevent the patient's symptoms based on specific clinical measures or visible results, should the healthcare system and the patient get their money back? A money-back guarantee might also be applicable if the patient suffers adverse effects from the treatment? Paying by outcome? HTA is "a multi-disciplinary field of policy evaluation studying the medical, economic, social and ethical implications of the development, diffusion and use of health technologies". HTA functions are: horizon screening, topic selection, assessment, appraisal, funding. *What do government purchasers want?* Government purchasers want and need more

certainty about the benefits and risks of medical technology and a reduction in the variation in use and outcomes.

- *How do payers consider the evidence of cost and effectiveness?*

The approach to evaluating costs and efficacy in the *Blue Cross and Blue Shield Association's Technology Evaluation Center (BCBSA - TEC)* has been recognized for its leadership in evidence-based healthcare technology assessment *(Frank Lefevre)*. Its mission is to provide healthcare decision makers with timely, objective, and scientifically rigorous assessments that synthesize the available evidence on the diagnosis, treatment, management and prevention of disease.

The technology must have final approval from the appropriate governmental regulatory bodies. The technology must improve the net health outcome. In 1991 recommendations from the NIH consensus panel were accepted: open gastric bypass and vertical banded gastroplasty met TEC criteria. In 2003 the evidence was sufficient to conclude that surgery improves health outcomes for patients with morbid obesity as compared to nonsurgical treatment: open gastric bypass was considered gold standard procedure. Other procedures did not meet TEC criteria. In 2005, laparoscopic gastric bypass met TEC criteria. In 2008 laparoscopic adjustable gastric banding (LAGB) met TEC criteria. The 2011 TEC Assessments states: efficacy of bariatric surgery for patients with lower BMI's with an emphasis on LAGB for patients with BMI < 35 (with comorbidities) or < 40 (without co-morbidities).

- *What about priorities for research in diabetic patients?*

Comparative studies, standardized and uniform definitions of outcomes, specific operations in specific patient groups.

Day 3: Keynote lectures by Joseph Goldstein and Michael Brown *(awarded by Nobel Prize in Physiology and Medicine in 1985 for their discoveries concerning the regulation of cholesterol metabolism).*

Surviving Starvation: Essential Role of the Ghrelin-Growth Hormone Axis was the topic. There is a changing dynamic in chronic diseases in the US. In adults > 50 years of age: CVD decreased by 60% from 1960 to 2010. Deaths /100,000 increased 2 fold, and diabetes 13 fold. Preclinical data suggest an inverse interaction of the orexogenic ghrelin (gastric) and the anorexogenic leptin (adipose tissue). Pre-pro-ghrelin, ghrelin and desacetil-ghrelin are active in releasing growth hormones (GH). The plasma profile of ghrelin represents a hunger signal to brain. *Excess ghrelin* increases appetite, food intake, and body weight. Loss of ghrelin or of ghrelin receptors has no effect on feeding or growth. Ghrelin O-aceyl transferase (GOAT) is the key enzyme. Co-localized with ghrelin in gastric mucosa, the essential function of Ghrelin is to maintain blood sugar by stimulating growth hormone release in times of famine. Appetite is due to an increase of ghrelin and its desacetilates. A sixty-per-cent calorie reduction decreases body weight and fat mass. Ghrelin increases in fasting and decreases after feeding (the same for desacetyl-ghrelin). Ghrelynoma cells increase production of ghrelin. Epinephrine stimulate ghrelin secretion; athenolol and resperine block it.

The emerging key issue: what is the role of the gut in the physiology and pathophysiology of obesity and diabetes?

- The conventional paradigm of the pathophysiology of obesity *(Rudolph Leibel)* stresses the importance of the fundamentals of the disease: genotype plus phenotype and correlation

between lean body mass and energy expenditure. Energy expenditure, energy intake, autonomics system, neuroendocrine system, and muscle cells are closely interconnected.
In the correlation between leptin and fat is the threshold changeable? Leptin mass is equal to cell size x number: *how much leptin is required to compensate resistance?* Prolonged weight reduction does not lower threshold.

- The conventional paradigm of the pathophysiology of diabetes *(Richard Bergman)* stresses the importance of beta cell function and insulin resistance. The product of insulin secretion and insulin sensitivity is a constant called disposition index (DI). This suggests that environmental reduction in insulin sensitivity such as obesity, pregnancy, or infection, will be countered by increase in insulin secretion which protects the system from the impairment stemming from glucose tolerance. *Does RYGB remove a gut factor which reduces glucose tolerance? Does this factor normally prevent postprandial hypoglycemia? Does it cause insulin resistance? Does it reduce beta-cell response (direct or through incretin?)? Does this factor act via portal receptors?*

- *Can factors from the gut significantly modulate food intake and blood glucose?*
*G*astro-entero-pancreatic hormones regulate food intake (*Jens Holst)*. They are represented by ghrelin, cholecystokinin (CKK), glucagon-like peptide-1(GLP-1), oxyntomodulin, peptide YY (PYY), amylin, pancreatic polypeptide (PP), glucagon, insulin. Seventy per cent of post-glucose insulin secretion is due to the incretin effect. Incretins amplify insulin secretion so that glucose excursions are kept constant. GLP-1 and GIP are secreted in response to meals in normal subjects stimulates insulin and reduces glucagon secretion in healthy subjects. In T2DM secretion of GLP-1 is impaired. Beta-cell sensitivity to GLP-1 is decreased and secretion of GIP slightly impaired; the impaired incretin response contributes significantly to the defective insulin secretion in T2DM. On the other hand incretin action could be restored by pharmacological amounts of GLP-1. Interventions associated with increased secretion of GLP-1 and other gut peptides may be useful for both obesity and diabetes.

- *What is the role of intestinal microbiota in insulin resistance, obesity, and diabetes?*
Trillion of bacteria *(Ruth Ley)*, derived from mother and environment, are active in the gut: they together represent the Microbiome. Alterations in host/microbiota interaction and microbial community composition/function produces low-grade inflammation , which promotes hyper-phagia and insulin resistance, and hyper-glycemia, hyper-insulinemia, hyper-lipidemia, obesity, and hypertension. Leptin levels correlate with bacterial population levels. Obese-associated microbiome has altered representation of bacterial genes.

- A progressive impairment of β-cell function and deterioration of glycemic control is described in type 2 diabetes *(David Cummings).* The incretin effect is the augmentation of insulin secretion beyond the effect of glucose alone. GLP-1 is secreted by L-cell (ileum), and gastric inhibitory polypeptide (GIP) is secreted by K-cell (jejunum), both of which enter in the stimulation of β-cell growth/mass. GLP-1 decreases glucagon and glucose levels in patients with type 1 diabetes. The major targets for GLP-1 are β-cell, α-cell, stomach, and nervous system; for GIP the targets are β-cell and adipose tissue. Normalization of fasting and postprandial glucose is achieved with intra venous GLP-1 in T2DM. A novel role of the gut is in the regulation of hepatic insulin sensitivity. *Are elevated GLP-1 levels after RYGB associated with an increased incretin effect?* A comparison of several surgery approaches in incretin secretion was described.

- *Could the GI tract be the missing link between obesity and diabetes?*

Francesco Rubino summarized the known fundamentals of the even more established link between the two diseases. Increases in BMI greatly affect the relative risk of developing type 2 diabetes. *Does obesity cause diabetes? Or does diabetes cause obesity?* The common cause could be the alteration of energy/glucose homeostasis. The question is how to build up a rationale for a role of the GI tract in diabetes (and obesity)? Arguments to support the rationale could be: epidemiology, physiology, pathophysiology, ex-adiuvantibus, bypass paradox, anti-incretin theory, and dysfunctional GI mechanisms in diabetes and obesity. A provocative yet reasonable hypothesis, is the GI tract an endocrine organ? RYGB effect on glucose tolerance, duodenal exclusion effects, incretin activities, anti-incretin therapy were again described in their mechanisms of action in diabetes and obesity. After the discoveries by Oskar Minkowsky in 1889, Frederick Banting and Charles Best in 1921, we are now facing a new understanding of the correlation among the reduction of weight, hepatic lipid content, hepatic TG content, and cellular mechanism of insulin resistance.

Take-home message

From the point of view of clinical practice, *Harold Lebovitz* recalled some key issues that should be taken in consideration. In defining appropriate surgical candidates for diabetes surgery, the major issues are: a) the inadequacies of BMI at least for subjects with BMI < 35; consider waist circumference or the criteria for metabolic syndrome; b) high baseline plasma insulin is the best predictor of benefit in reducing CV events; c) left ventricular volume and other CV markers identify those patients who would benefit from bariatric surgery; d) discussion concerning the value of bariatric surgery for diabetic patients who already have significant vascular complications. In defining and measuring success of surgical treatments for diabetes, the major questions are: a) should success be defined by surrogate markers or clinical outcomes?; b) do we have sufficient data on clinical outcomes?; c) how practical is the time required in the pharmacological sector to identify outcomes of clinical studies?; d) do improvements in surrogate markers always predict clinical benefits, e.g. in vascular disease, retinopathy, nephropathy; e) which one is a more reliable outcome for diabetes control: remission? HbA1C < 7 %? reduction in diabetes medications? quality of life? reduction of sleep apnea?

What about Guidelines

There is a need to reconcile guidelines*,* said *Paul Zimmet,* and to consider issues in different nations, in different organizations, institutions; also between different professionals within organizations.

The *International Diabetes Federation (IDF) Position Statement* is an answer to the escalation of type 2 diabetes epidemic that strongly correlates with increases in obesity and physical inactivity. There is a need for strategies to prioritize severely obese persons with type 2 diabetes to ensure that surgical interventions are available to those most likely to benefit.

Bariatric surgery is an appropriate treatment for people with type 2 diabetes and obesity who have not achieved the recommended treatment targets with medical therapies, especially when there are other major co-morbidities. Surgery should be an accepted option in people who have type 2 diabetes and BMI of 35 or more….

Surgery should also be considered as an alternative treatment option in persons with BMI 30 to 35 when diabetes cannot be adequately controlled by optimal medical regimen, especially in the presence of other major cardiovascular disease risk factors. In Asian, and some other ethnicities of increased risk, BMI action points may be lower, e.g. BMI 27.5 to 32.5…..
Surgical management for type 2 diabetes must be performed within accepted international and national guidelines. This requires appropriate assessment for the procedure, comprehensive and ongoing multidisciplinary care, patient education, follow-up and clinical audit, as well as safe and effective surgical procedures, national guidelines for bariatric surgery in people with type 2 diabetes…..
Research recommendations: establish better criteria than BMI for predicting benefit from surgery, and define which patients benefit most from which procedures. Studies are needed: to establish the benefit of surgery for persons with diabetes and BMI less than 35; to establish the duration of the benefit of surgery: and to establish the mechanisms of the success of surgery. New techniques should be assessed rigorously for efficacy and safety. Studies are needed to define the best regimens of diabetes management after bariatric surgery. RCTs are needed to evaluate and compare different bariatric procedures for the treatment of diabetes between themselves as well as emerging non-surgical therapies.

Public Health Policies

There is the need for an agreement in the practical implementation of guidelines *(David Flum),* taking in consideration: evidence needed to make changes; feasibility-economics; and resource availability. The goal is the right intervention, in the right patient, at the right time. It is important to recognize competing demands of competing systems: capacity exceeds demands, demand exceeds capacity.

The Evolving Paradigm of Diabetes Pathogenesis

Jesse Roth noted more questions raised during the meeting:
Will we replace surgery with medication? Will we understand more on the signaling between anti - inflammatory and pro-inflammatory adipose cells? Will we understand more on the collaboration between microbioma and human genoma? Will we know more on the seeding of obesity and diabetes, its germinating at conception, early in-utero, late in-utero, and early post-natal periods? Can we develop appropriate programs to protect against early influences that lead to obesity and diabetes later in life?
" We need to act much earlier to recognize pathology and to intervene. There now exist strategies to diagnose and treat these promoters of pathology at very early stages. We particularly recommend phasing out "normal" ranges based on population values: replace "normal" ranges by "personalized" targets for each individual, based on physiology".

Corollary

It should not be surprising to observe such a central role of metabolic processes and the integration of metabolic pathways with many diverse signal transduction pathways in non communicable diseases (NCD). A better understanding of the shared metabolic pathways might support a global approach to their prevention and treatment. This approach could also help form

strategic policies to tackle the disease burden and to develop an action plan for the global strategy for the prevention and control of non-communicable diseases to work in partnership to prevent and control the 4 primary non-communicable diseases — *cardiovascular diseases, diabetes, cancers, and chronic respiratory diseases* - and the 4 shared risk factors: tobacco use, physical inactivity, unhealthy diets and the harmful use of alcohol, all four of which heavily impact the metabolic mechanisms of the body.
http://www.healtheurope.org/index.php?option=com_content&task=view&id=186&Itemid=0