Double Diabetes: Definition, Diagnosis, Treatment, Prediction and Prevention.

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ALAD 2007 CONGRESS
Prevalence of OVERWEIGHT and OBESITY in the young

Modified from Lobstein T, Frelut M-L., 2003
The problem of defining types of diabetes

Differences between type 1 and type 2 diabetes are not always straightforward and in many cases common pathogenic processes may operate.

Even the best animal model of type 1 diabetes (NOD mouse) has some genetic background that can predispose to insulin resistance before the destruction of beta cells and in absence of hyperglycaemia.

These observations suggest that non immunological processes may also be important in the cascade of events leading to beta cell destruction and, conversely, an immune mediated process can accelerate β cell failure in type 2 diabetes.
What is Double Diabetes?
Case Report

Coexistence of type 1 and type 2 diabetes mellitus: “double” diabetes?

Libman IM, Becker DJ. Coexistence of type 1 and type 2 diabetes mellitus: double diabetes?

Ingrid M. Libman and Dorothy J. Becker
Division of Pediatric Endocrinology, Department of Pediatrics, Children’s Hospital of Pittsburgh, Pittsburgh, PA
DOUBLE DIABETES (DD) is characterized by the occurrence of hyperglycaemia in children and young adolescents with the combination of markers typical of both type 1 and type 2 diabetes.
Little is known on prevalence however

- OBESITY + METABOLIC SYNDROME
- AUTOIMMUNITY to beta cell
- COMPLICATIONS ASSOCIATED WITH LOSS OF BETA CELL FUNCTION, including hypoglycaemia, ketoacidosis, difficult management of the disease
- MICROVASCULAR COMPLICATIONS in addition to macrovascular complications typically associated with T2D
Beta cell autoantibodies were detectable in a subgroup of initially non-insulin requiring diabetic children and adolescents with the clinical appearance of T2D.
Prevalence of DOUBLE DIABETES in Germany and Italy

Prevalence double diabetes → 32%

Lazio region (Italy):
101 consecutive cases of diabetes (age 5-30 yrs)

Prevalence double diabetes:
Group 15-30 yrs: 16.2%
Group 5-15 yrs: 23.6%

OVERALL PREVALENCE 19.7%

ß-cell autoantibodies in children with type 2 diabetes mellitus: subgroup or misclassification?
T Reinehr, E Schober, S Wiegand, A Thon, R Holl and on behalf of the DPV-Wiss Study Group
Arch. Dis. Child. 2006;91:473-477; originally published online 31 Jan 2006; doi:10.1136/adc.2005.088229
Clinical and pathogenic features of Double Diabetes in between type 1 diabetes and type 2 diabetes

<table>
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<tr>
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<th>Type 1 Diabetes</th>
<th>Double Diabetes</th>
<th>Type 2 Diabetes</th>
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<tbody>
<tr>
<td>AGE AT DISEASE ONSET</td>
<td>Childhood +++</td>
<td>Childhood ++</td>
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<td>Adolescence +++</td>
<td>Adolescence ++</td>
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<td></td>
<td>Adult +</td>
<td>Adult (LADA) +</td>
<td>Adult +++</td>
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<td>MAJOR GENETIC</td>
<td>HLA class I and II, Ins VNTR, CTLA-4</td>
<td>?</td>
<td>AMP1, PPR γ -2</td>
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<td>PREDISPOSITION</td>
<td>PTPN 22, ?</td>
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<td>PC-1, TCF7L2</td>
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<td>ENVIRONMENTAL</td>
<td>Diet, viruses</td>
<td>Life style</td>
<td>Life style</td>
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<td>FACTORS</td>
<td>Cow’s milk</td>
<td>(diet, sedentary life)</td>
<td>(diet, sedentary life)</td>
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<td>Type 1 Diabetes</td>
<td>Double Diabetes</td>
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<td>CIRCULATING ABS TO β CELLS</td>
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<td>T-CELL MEDIATED IMMUNITY TO β CELLS</td>
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<td>C-PEPTIDE SECRETION</td>
<td>-</td>
<td>+</td>
<td>+++</td>
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<td>INSULIN RESISTANCE</td>
<td>- or +</td>
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<td>+++</td>
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<td>INFLAMMATORY MARKERS</td>
<td>+</td>
<td>++</td>
<td>+++</td>
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<td>MACRO-VASCULAR COMPLICATIONS</td>
<td>+</td>
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Once hyperglycaemia has developed in an obese child or adolescent, recognition of the type of diabetes may pose problems. Generally an increased “METABOLIC LOAD” and a reduced “AUTOIMMUNE LOAD” are features of DD.

Tipically, Double Diabetes is characterized by:

- Insulin resistance
- Obesity
- Markers of beta cell autoimmunity
Clinical and biochemical parameters to diagnose a youth with DD

- Presence of clinical features of T2D
- Hypertension
- Dyslipidemia
- Increased BMI with increased cardiovascular risk compared with children with classical T1D
- Family history for T2D and T1D may be present
Presence of a reduced number of clinical features typical of T1D such as weight loss, polyuria/polydipsia, and insidious onset of ketoacidosis.

Insulin therapy is not the first line of therapy compared with subjects with classical T1D.

Presence of autoantibodies to islet cells but with reduced number and titer compared to T1D.

Probably reduced risk at HLA locus compared with subjects with T1D.

DD is always characterized by an OBESE PHENOTYPE WITH THE ADDITION OF COEXISTENCE OF BETA CELL AUTOIMMUNITY.
DOUBLE DIABETES
as one end of the rainbow
of Type 2 Diabetes

Pozzilli P & Buzzetti R, Trends Endocrinol Metab. 2007
Consistent beta cell function is still present at the time of diabetes diagnosis.

Decline of beta cell function may be slower than in classical T1D.

Insulin resistance is present.

A treatment capable of interfering with the putative mechanisms involved in the disease process should be considered.

What THERAPY for Double Diabetes?
Diet

Physical activity

Metformin

Insulin

+others
Diet and physical exercise regimens have shown significantly greater effect in preventing the onset of T2D compared to placebo (58% decrease in incidence), and changes in lifestyle were even superior to metformin therapy (31% decrease in incidence).

Whether such approach may be successful in DD where, autoimmune phenomena also play a major role is unknown.

Recommendations for Managing Body Weight in Youths with or at risk of Type 2 Diabetes (I)

**Food modification** (for weight control and blood glucose control)

- Individualize calorie and food intake based on age, sex, and physical activity.
- Limit consumption of snacks that have high levels of fat, sugar or salt (e.g. potato chips, fast food, soda, desserts).
- Provide a meal plan developed by a registered dietitian, diabetes educator or physician that includes low-fat and high-fiber foods, small portion sizes, and fewer beverages with high sugar content.
- Teach the patient and family how carbohydrates can effect blood glucose level.

US Department of Agriculture. Dietary guidelines for Americans 2005
Recommendations for Managing Body Weight in Youths with or at Risk of Type 2 Diabetes (II)

Physical activity (for weight control and improvement in insulin sensitivity)

- Prescribe 30 to 60 minutes of physical activity per day
- Limit television and video game time to one or two hours per day

US Department of Agriculture. Dietary guidelines for Americans 2005
Diet and exercise alone are effective for metabolic control in less than 10 percent of youths with type 2 diabetes.

Kaufman FR et al. J Pediatr Endocrinol Metab 2002

Adjunctive metformin in overweight young people with T1DM improves glycaemic control without the weight gain expected with insulin therapy [...] In long term, insulin treatment was associated with a fall in BMI.

Moon RJ et al. Diabetes, Obesity and Metabolism. 2007
Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes.
Specifically in patients with preserved beta cell function and a high GADA titer at the initiation of insulin.

The TOKYO STUDY IN LADA: SMALL DOSES OF INSULIN FOR PREVENTION OF BETA CELL DESTRUCTION

INSULIN group
C-peptide +
Anti GADA +
58.3%

SU group
C-peptide +
Anti GADA +
0%

p<0.001

RETENTION OF BETA CELL FUNCTION (C-PEPTIDE)

Specifically in patients with preserved beta cell function and a high GADA titer at the initiation of insulin.

Diet
Physical activity
Metformin
Insulin
+others
Other pharmacological options for treatment of Double Diabetes

- Orlistat
- Sibutramine
- Glucosidase inhibitors
- Thiazolidinediones
- Glucagon-like peptide-1
Treatment of comorbidities in Double Diabetes

- Hypertension
- Dyslipidemia
Blood Pressure

- Hypertension is defined as an average systolic or diastolic blood pressure greater than the 95\(^{\circ}\) percentile for age, sex, and height measured on at least three separate days.

- Angiotensin-converting enzyme inhibitors are preferred in children.
Recommendations for Monitoring Blood Pressure and Lipid Levels in Youths (II)

Lipids

- Optimal levels are: LDL <100 mg/dl; HDL >35 mg/dl; TG <150 mg/dl

- A lipid profile should be obtained at diagnosis, after glucose control is established; if lipid are at optimal levels, repeat lipid profile every three to five years

- If the LDL level is >100 mg/dl, prescribe an exercise plan and healthy diet; if goal are not reach after 6 months, consider statin therapy for patients with LDL of 130 to 159 mg/dl, and begin medications in patients with LDL >160 mg/dl

- Weight loss, increased physical activity and improved glycemic control often lead to improved lipid levels.

ADA. Standards of Medical Care in Diabetes-2006. Diabetes Care 2006
Prediction/Diagnosis and Prevention of Double Diabetes

Prediction/Diagnosis
- Perform OGTT in obese and overweight youths, especially those with family history for diabetes
- Measure autoantibodies to islet cells in subjects with impaired OGTT

Prevention
- Diet
- Physical activity
- Metformin
- Insulin
Double Diabetes

More studies on prevalence of DD in different ethnic groups

Better characterization (genetic, immunological, metabolic) of this form of diabetes

Follow-up studies aimed at preventing beta cell failure.

Trials using different approaches to find out what is the best therapy for treating hyperglycaemia in these patients.