

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

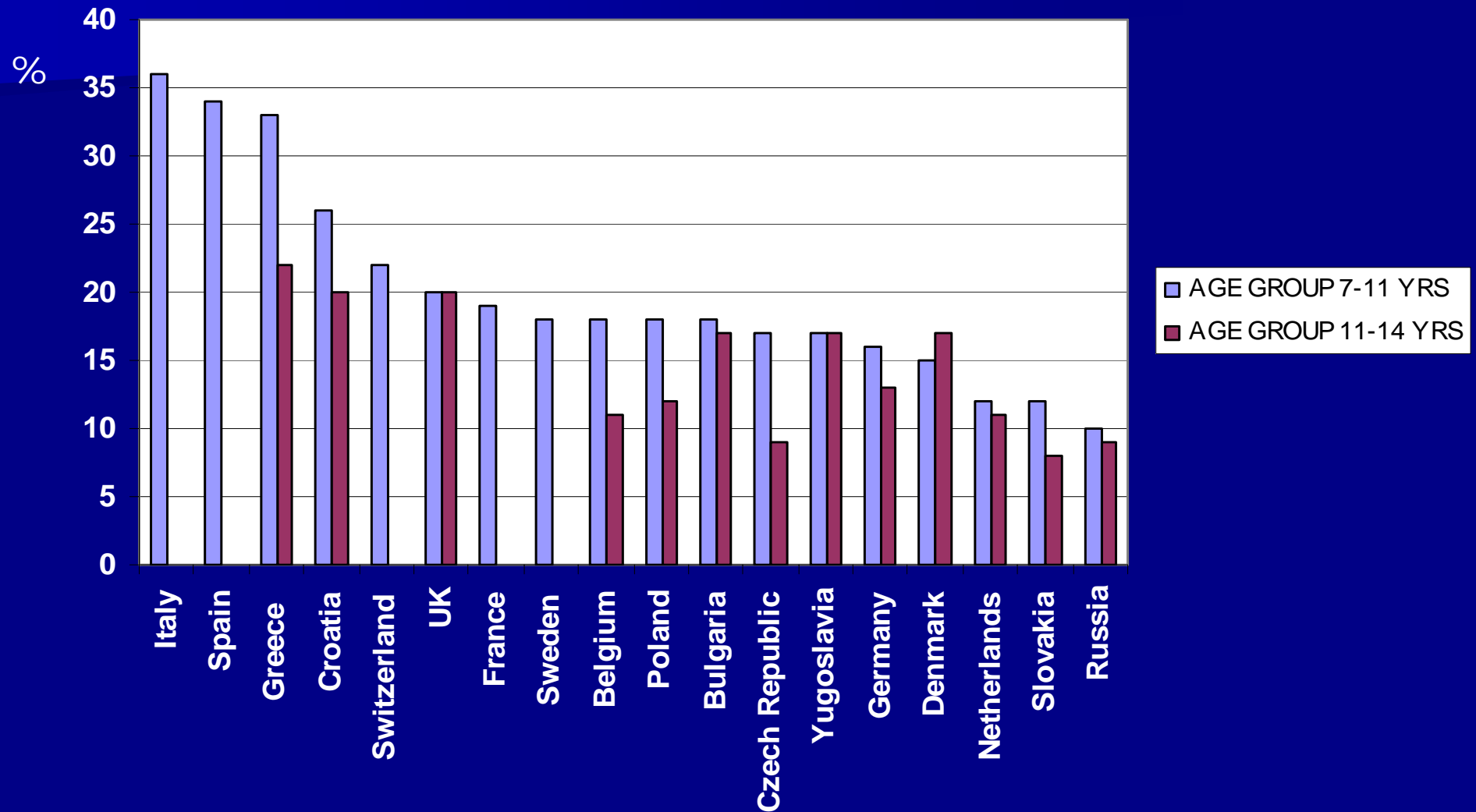
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*ALAD 2007 CONGRESS*

# 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  $\beta$  cell failure in type 2 diabetes.

# **What is Double Diabetes?**

*Pediatric Diabetes 2003; 4: 110–113  
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**Pediatric Diabetes**  
*ISSN 1399-543X*

## **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?  
*Pediatric Diabetes 2003; 4: 110–113. © Blackwell Munksgaard, 2003.*

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# **DOUBLE DIABETES**

**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.**

# Prevalence of DOUBLE 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

## **β-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

**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

**β-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

**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%**

# Clinical and pathogenic features of Double Diabetes in between type 1 diabetes and type 2 diabetes

	Type 1 Diabetes	Double Diabetes	Type 2 Diabetes
AGE AT DISEASE ONSET	Childhood +++ Adolescence +++ Adult +	Childhood ++ Adolescence ++ Adult (LADA) +	Childhood + Adolescence ++ Adult +++
MAJOR GENETIC PREDISPOSITION	HLA class I and II, Ins VNTR, CTLA-4 PTPN 22,	?	AMP1, PPR $\gamma$ -2 PC-1, TCF7L2
ENVIRONMENTAL FACTORS	Diet, viruses Cow's milk	Life style (diet, sedentary life)	Life style (diet, sedentary life)

	Type 1 Diabetes	Double Diabetes	Type 2 Diabetes
CIRCULATING ABS TO $\beta$ CELLS	+++	+	-
T-CELL MEDIATED IMMUNITY TO $\beta$ CELLS	+++	++	-
C-PEPTIDE SECRETION	-	+	+++
INSULIN RESISTANCE	- or +	++	+++
INFLAMMATORY MARKERS	+	++	+++
MACRO-VASCULAR COMPLICATIONS	+	++	+++

# Diagnosis of Double Diabetes

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

Typically, Double Diabetes is characterized by:

- **Insulin resistance**
  - **Obesity**
- **Markers of beta cell autoimmunity**

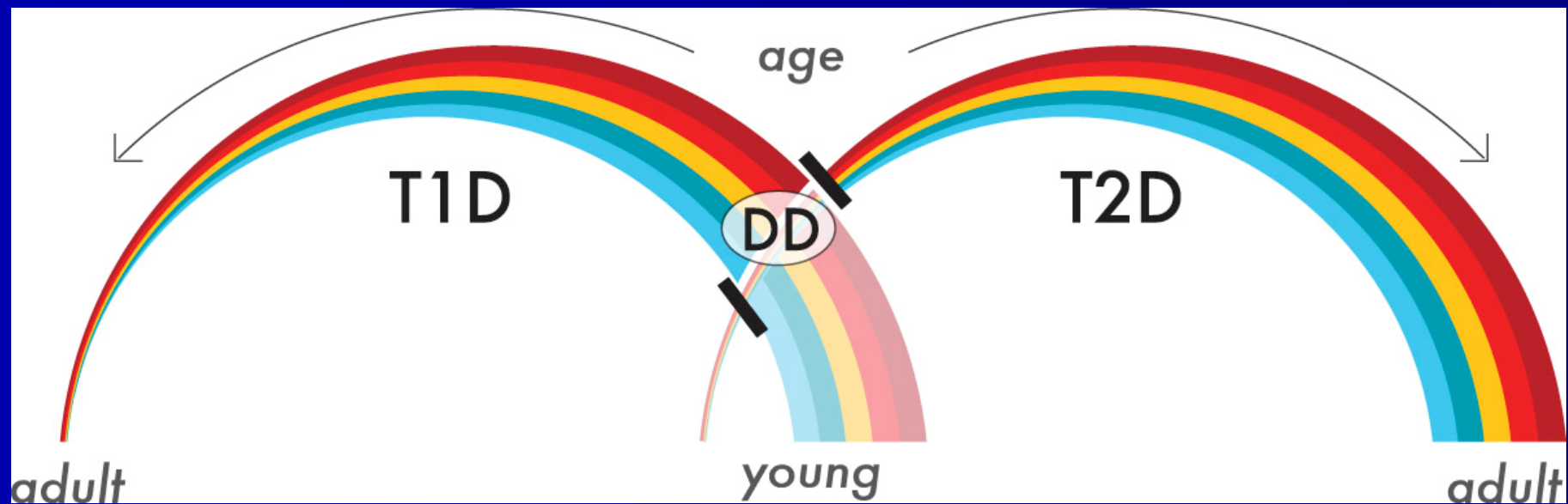
# **Clinical and biochemical parameters to diagnose a youth with DD**

- **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, insurgence of ketoacidosis
- Insulin therapy is not the first line of therapy compared with subjects with classical T1D
- Presence of autoantibodies to islet cells but 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



# What THERAPY for Double Diabetes ?

- 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.



**Diet**

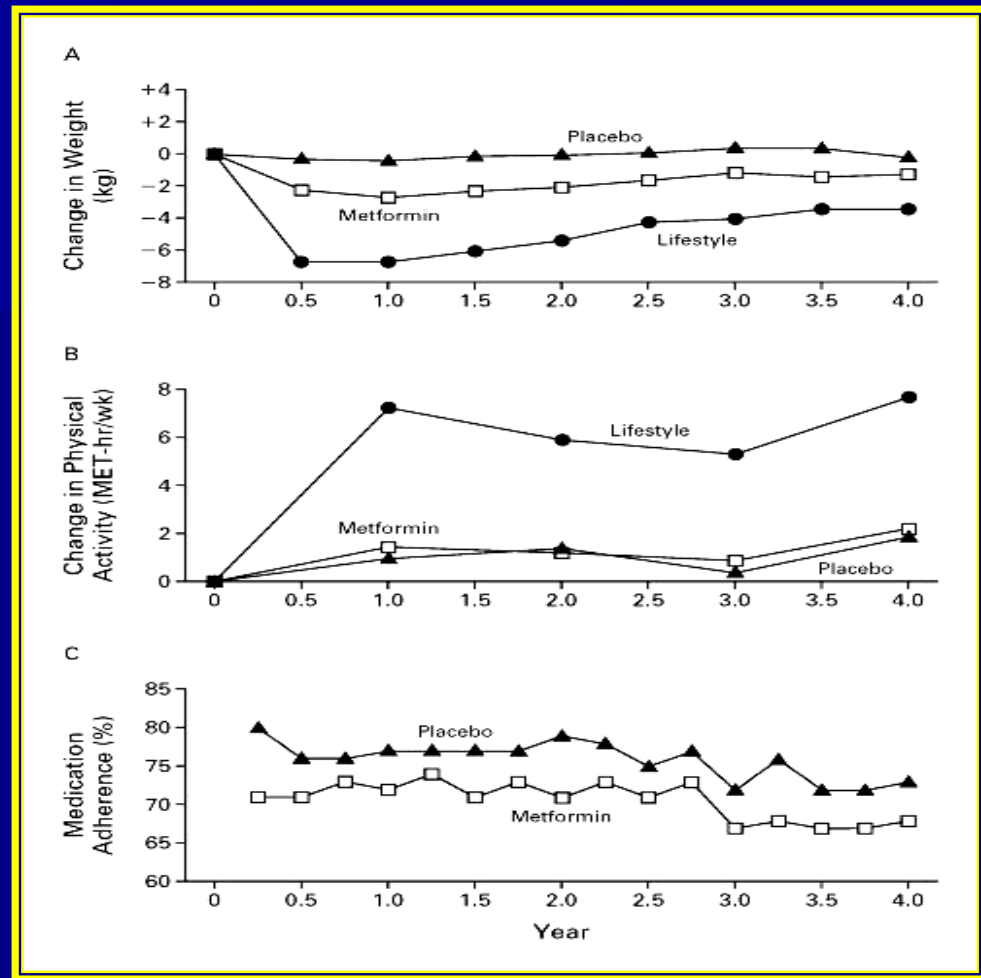
**Physical activity**

**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.

# 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

**Diet**

**Physical activity**

**Metformin**

**Insulin**

**+others**

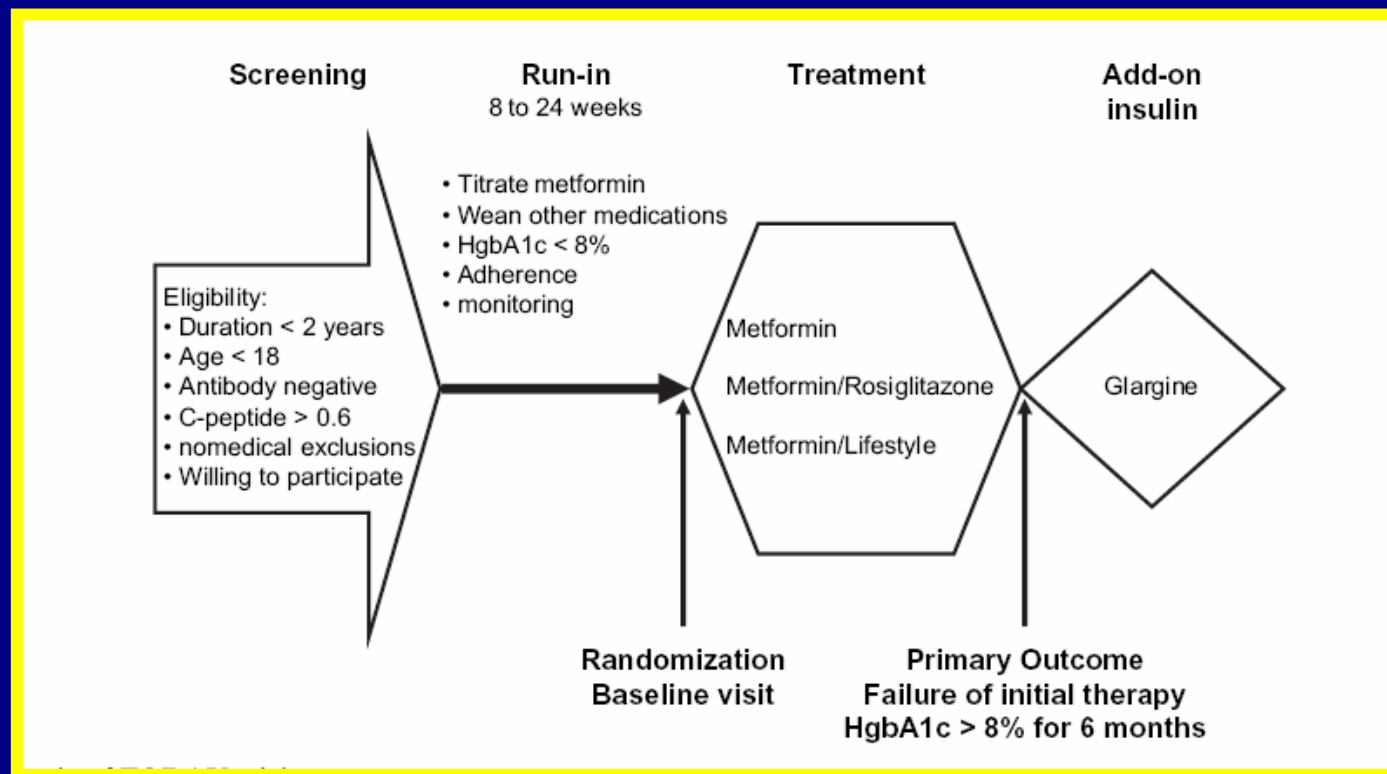
**Diet and exercise alone are effective for metabolic control in less than 10 percent of youths with type 2 diabetes.**

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



**Diet**

**Physical activity**

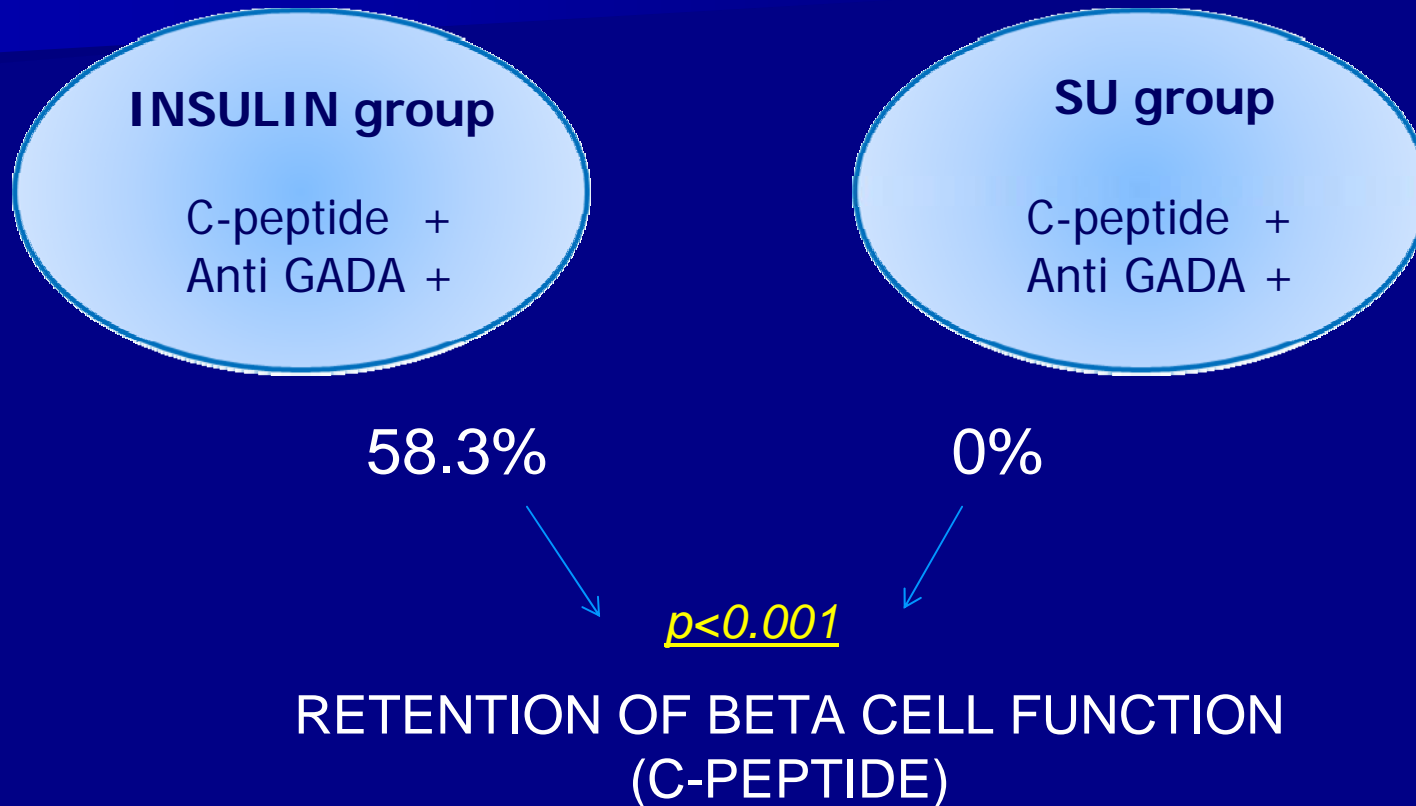
**Metformin**

**Insulin**

**+others**



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



*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**

# Recommendations for Monitoring Blood Pressure and Lipid Levels in Youths (I)

## Blood Pressure

- Hypertension is defined as an average systolic or diastolic blood pressure greater than the 95<sup>th</sup> 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.

# 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.

