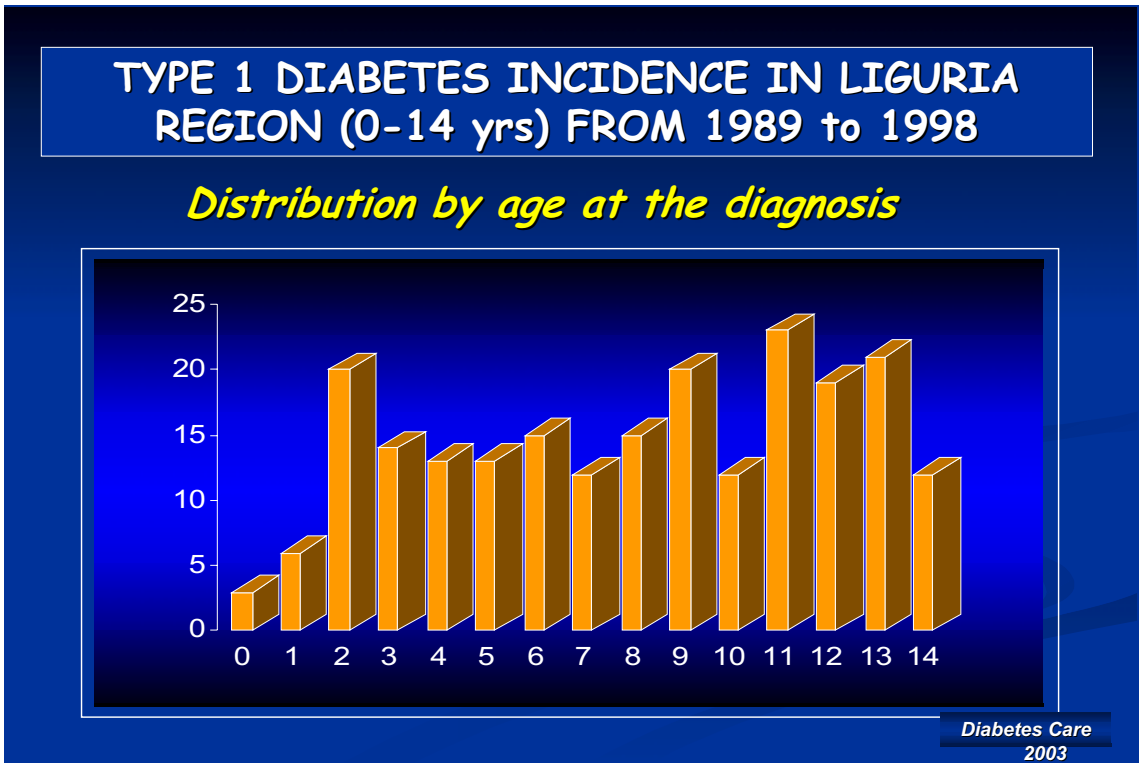
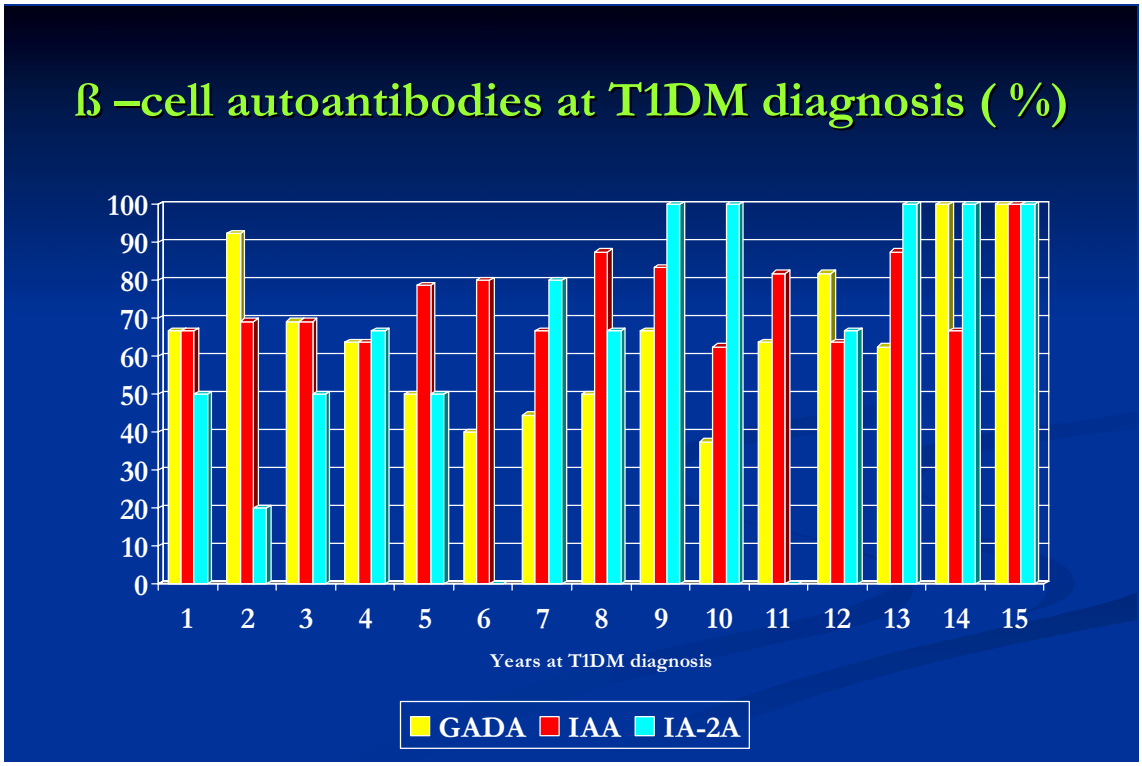
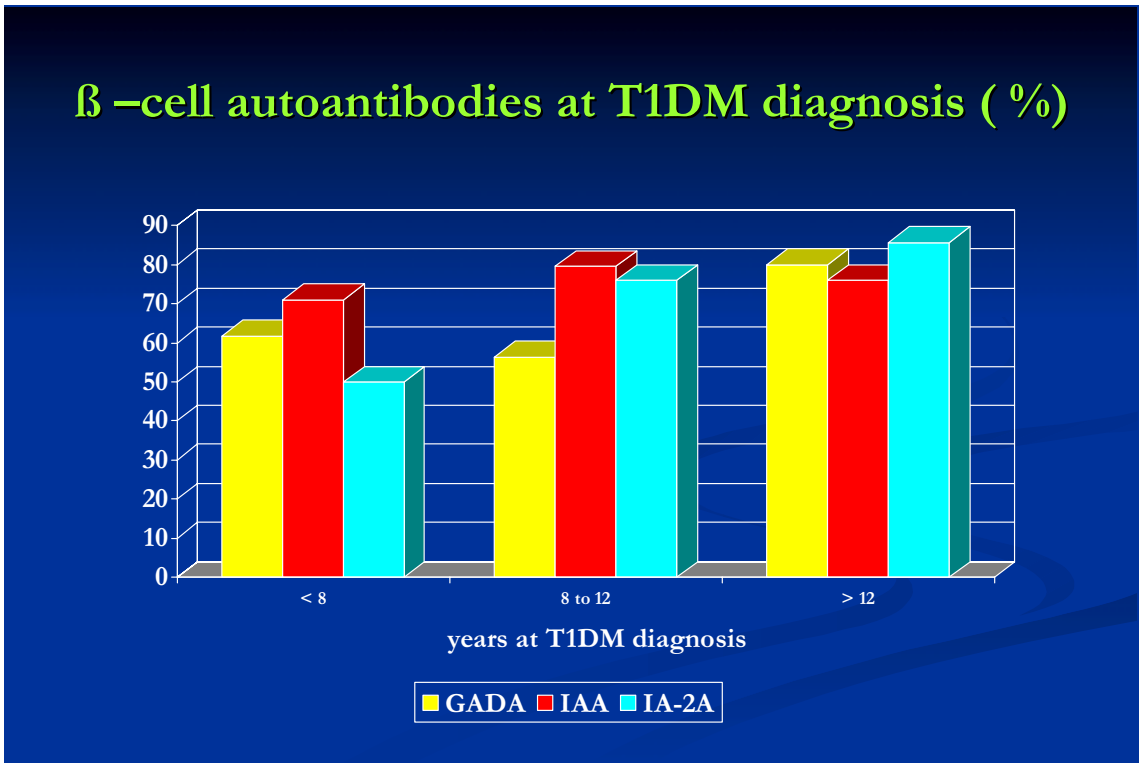
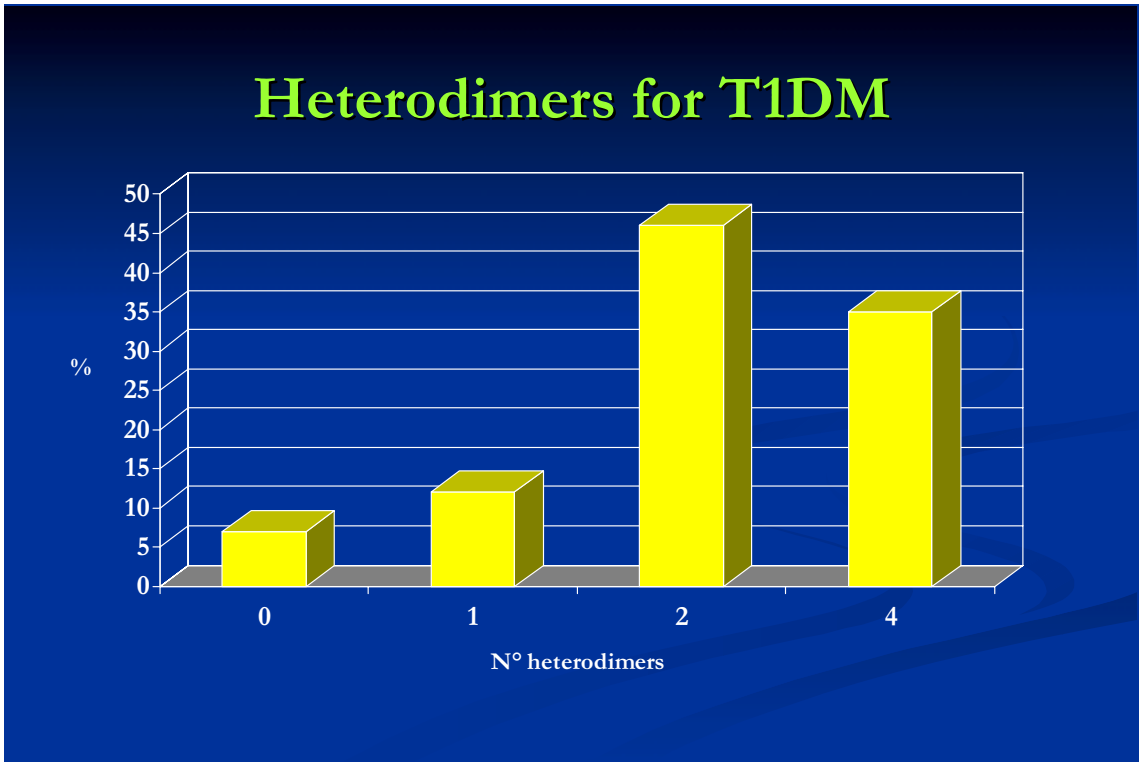
E3

WORKSHOP III






ß –cell autoantibodies at T1DM diagnosis (%)
90
80
70
60
50
40
30
20
10
0
< 8
8 to 12
> 12
years at T1DM diagnosis
GADA
IAA
IA-2A


Heterodimers for T1DM
%
50
45
40
35
30
25
20
15
10
5
0
0
1
2
4
N° heterodimers

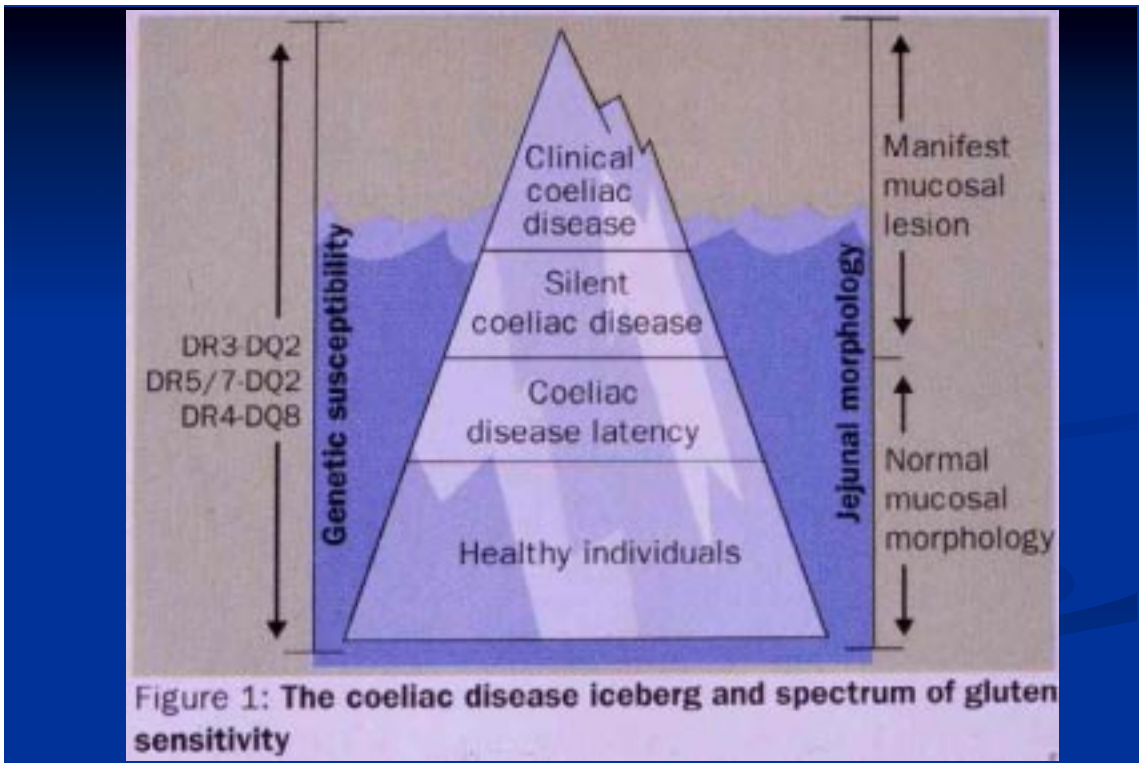
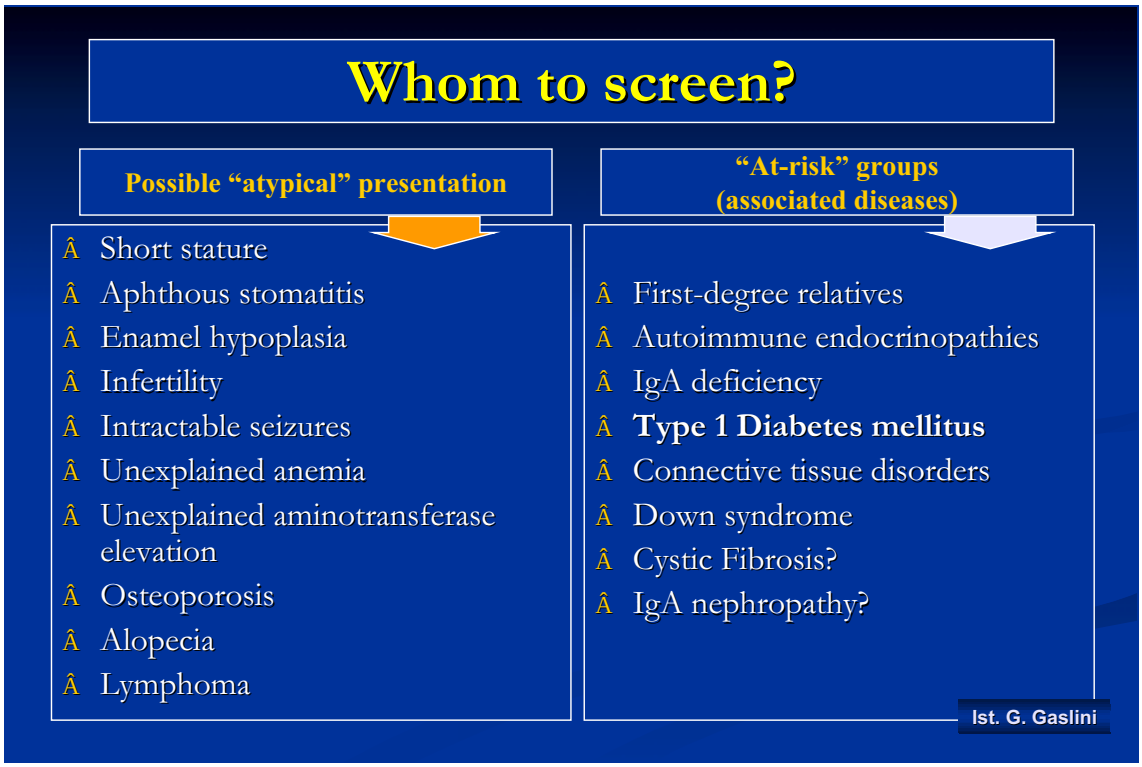
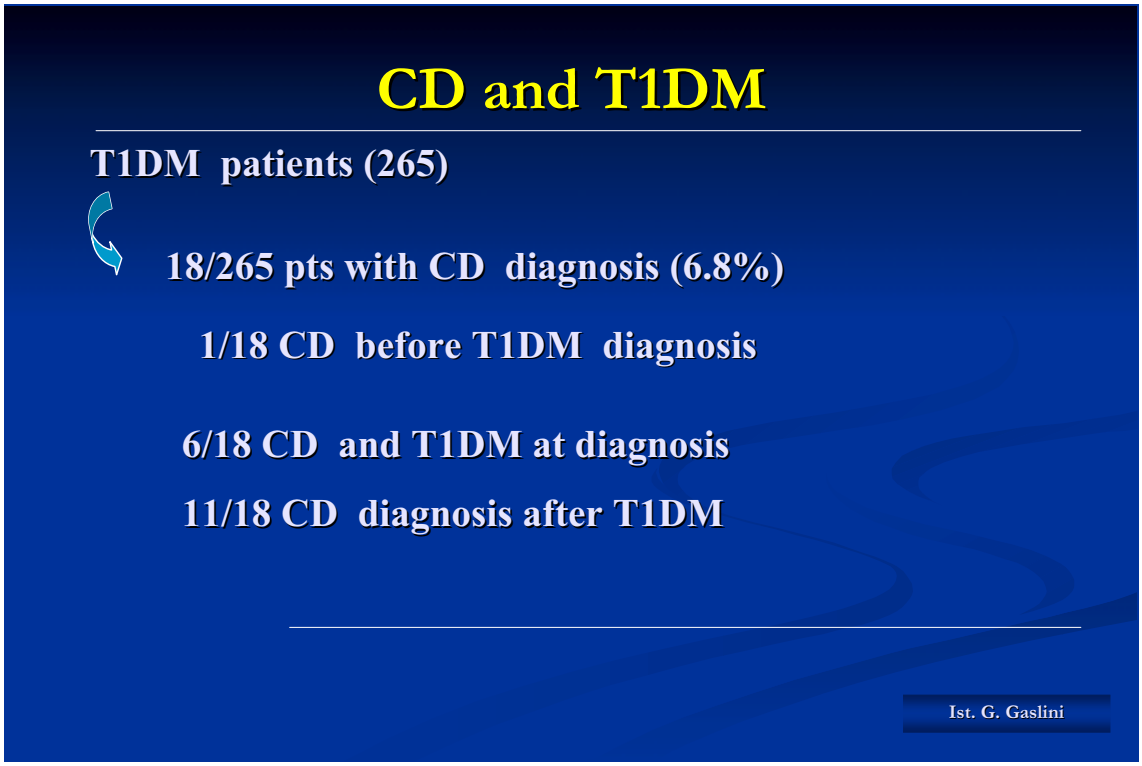


Figure 1: **The coeliac disease iceberg and spectrum of gluten sensitivity**

Fig. 2. Crude cumulative incidence rates of coeliac disease calculated on the basis of the whole material for each area.


Whom to screen?
Possible "atypical" presentation
Short stature
Aphthous stomatitis
Enamel hypoplasia
Infertility
Intractable seizures
Unexplained anemia
Unexplained aminotransferase elevation
Osteoporosis
Alopecia
Lymphoma
"At-risk" groups (associated diseases)
First-degree relatives
Autoimmune endocrinopathies
IgA deficiency
Type 1 Diabetes mellitus
Connective tissue disorders
Down syndrome
Cystic Fibrosis?
IgA nephropathy?
Ist. G. Gaslini


CD and T1DM
T1DM patients (265)
18/265 pts with CD diagnosis (6.8%)
1/18 CD before T1DM diagnosis
6/18 CD and T1DM at diagnosis
11/18 CD diagnosis after T1DM
Ist. G. Gaslini

Prevalence of ATA in different populations with T1DM

T1DM overall	7-40%
USA (North-American White pts)	20-30%
European	6-14%
USA (North-American Black pts)	4-5%
Chinese	0%

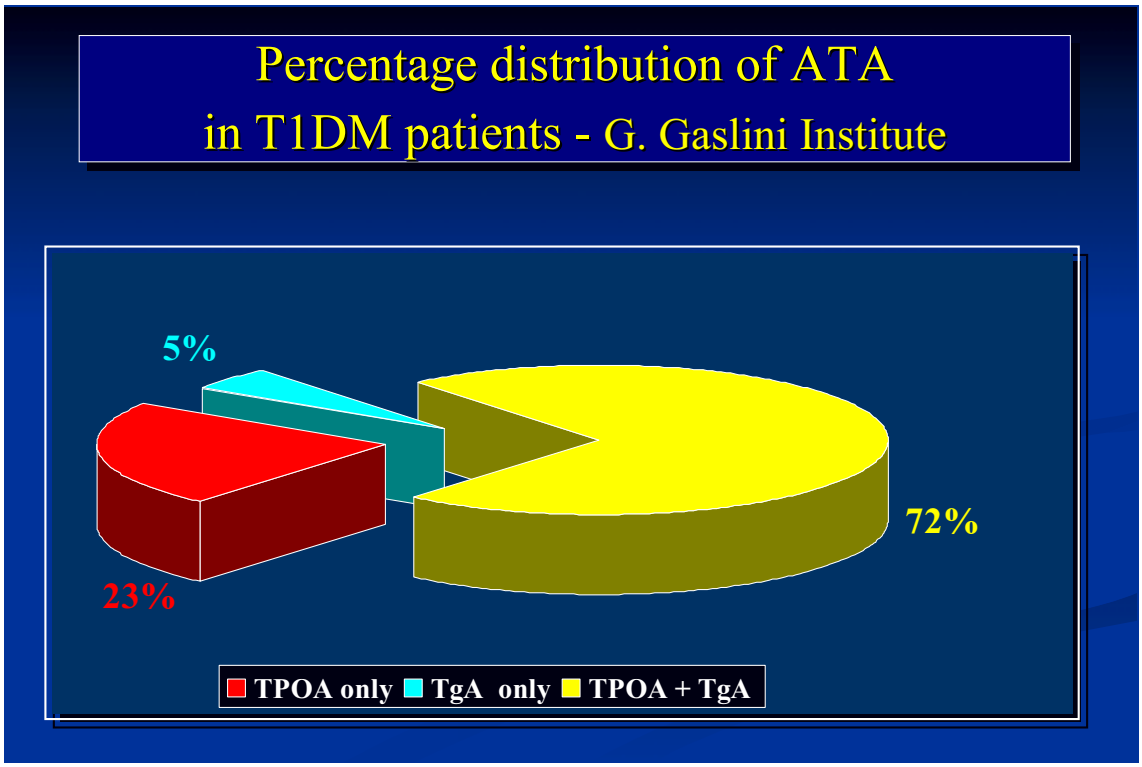
T1DM and autoimmune thyroid disease

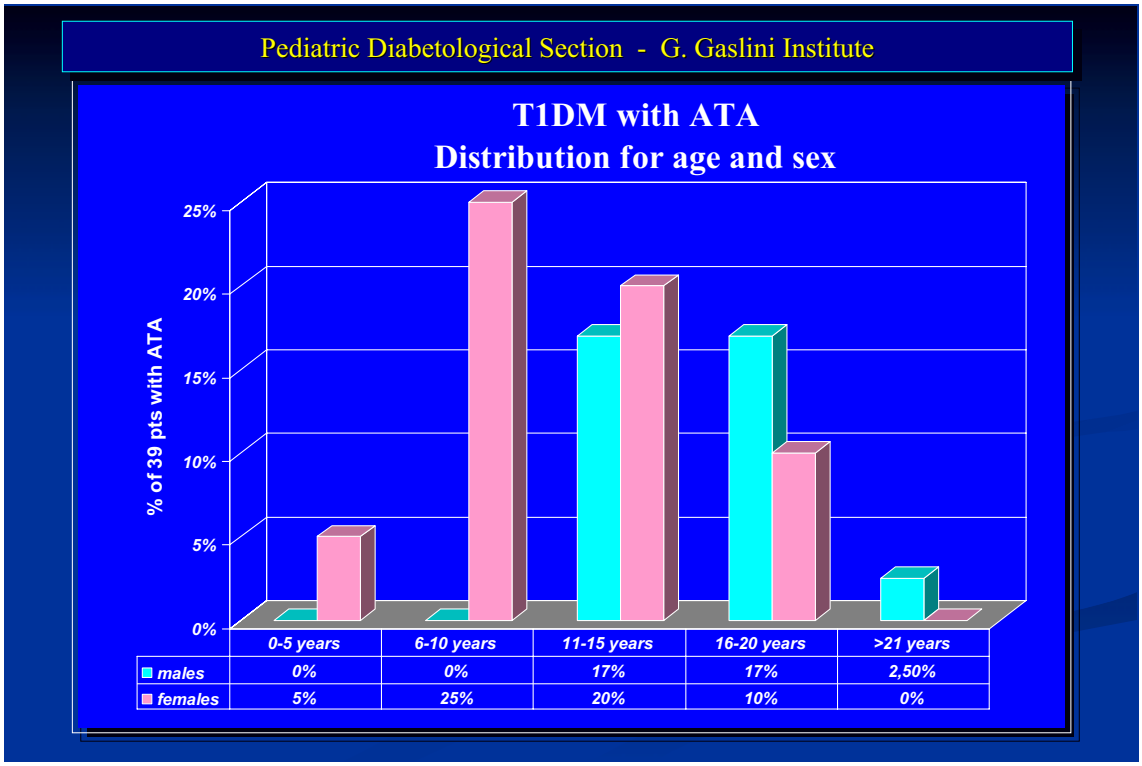
G. Gaslini Institute

Patients evaluated
169 M and 156 F

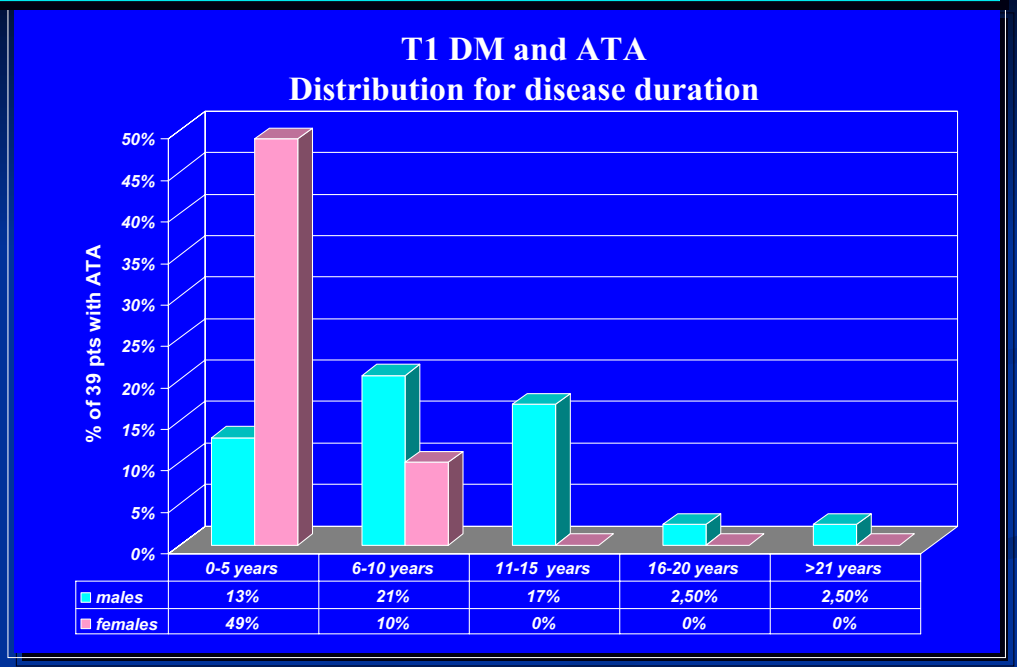
Pts with ATA
39 (12%)

Pts without ATA
286 (88%)

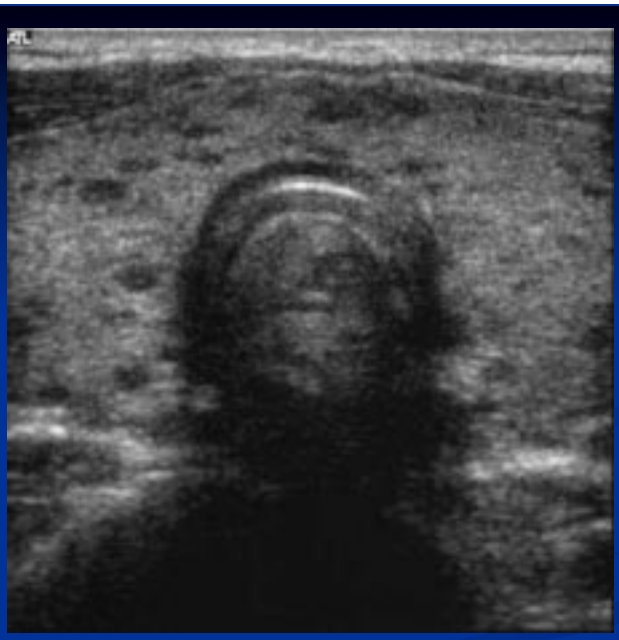

Percentage distribution of ATA
in T1DM patients - G. Gaslini Institute
5%
72%
23%
TPOA only
TgA only
TPOA + TgA


Pediatric Diabetological Section - G. Gaslini Institute
T1DM with ATA
Distribution for age and sex
% of 39 pts with ATA
25%
20%
15%
10%
5%
0%
0-5 years
6-10 years
11-15 years
16-20 years
>21 years
males 0% 0% 17% 17% 2,50%
females 5% 25% 20% 10% 0%

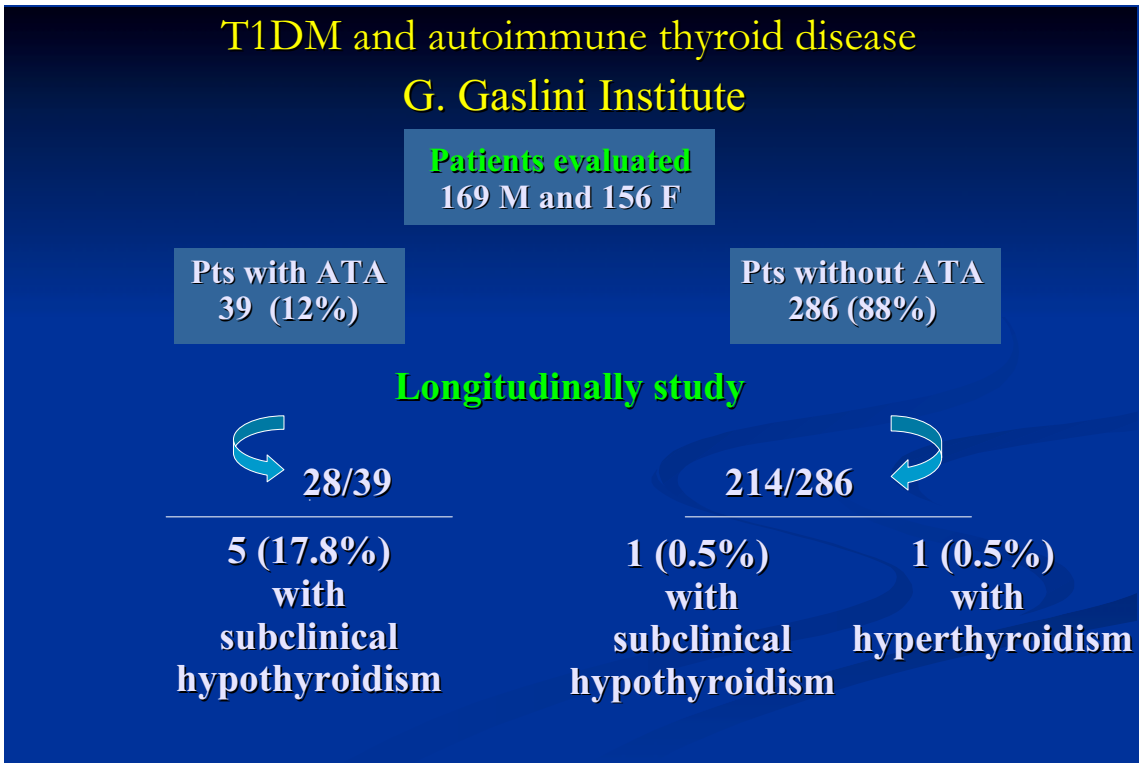
Pediatric Diabetological Section - G. Gaslini Institute

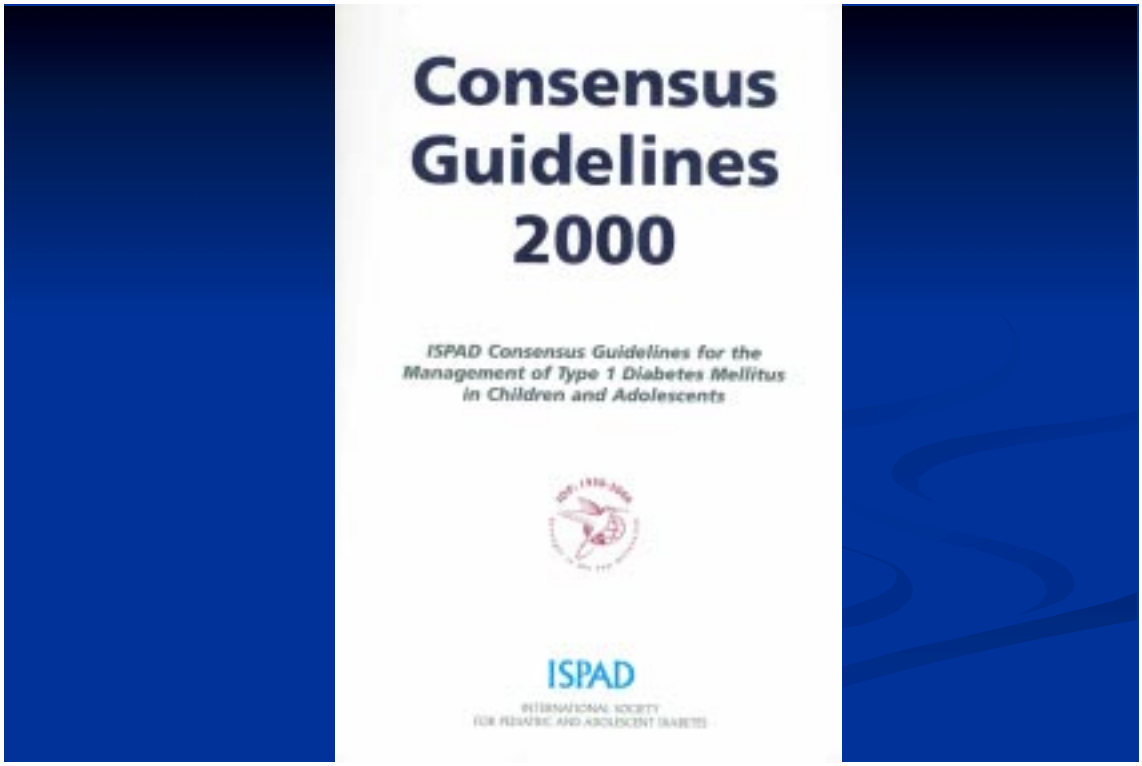


	0-5 years	6-10 years	11-15 years	16-20 years	>21 years
males	13%	21%	17%	2,50%	2,50%
females	49%	10%	0%	0%	0%



Transverse sonogram section of left lobe showing enlarged gland, diffuse hypoechogenecity with pseudonodularity


T1DM and autoimmune thyroid disease
G. Gaslini Institute
Patients evaluated
169 M and 156 F
Pts with ATA
39 (12%)
Pts without ATA
286 (88%)
Longitudinally study
28/39
214/286
5 (17.8%)
with
subclinical
hypothyroidism
1 (0.5%)
with
subclinical
hypothyroidism
1 (0.5%)
with
hyperthyroidism


Consensus
Guidelines
2000
ISPAD Consensus Guidelines for the
Management of Type 1 Diabetes Mellitus
in Children and Adolescents
ISPAD

Patient Management

- At diagnosis
  - hospital admission for ketoacidosis
  - insulin therapy
  - educational intervention
    - intensive insulin regimen
    - self monitoring of the disease
    - data recording in a log book
  - adequate food plan
  - regular physical activity

Type 1 diabetic young patient follow-up

- *Once-twice monthly examination*
  - blood tests, HbA1c, urynalisis
  - clinical check-up
  - auxological examination
  - dietician
  - new insulin protocol

Goals for physician

- *Clinical goals:*
  - to provide an effective treatment leading to a good glycemic control (HbA1c < 7,5%)
  - to delay the onset and/or slow down the progression of chronic complications;
  - to achieve a careful balance between insulin therapy, diet and physical activity;
  - to support continuous education of patients.

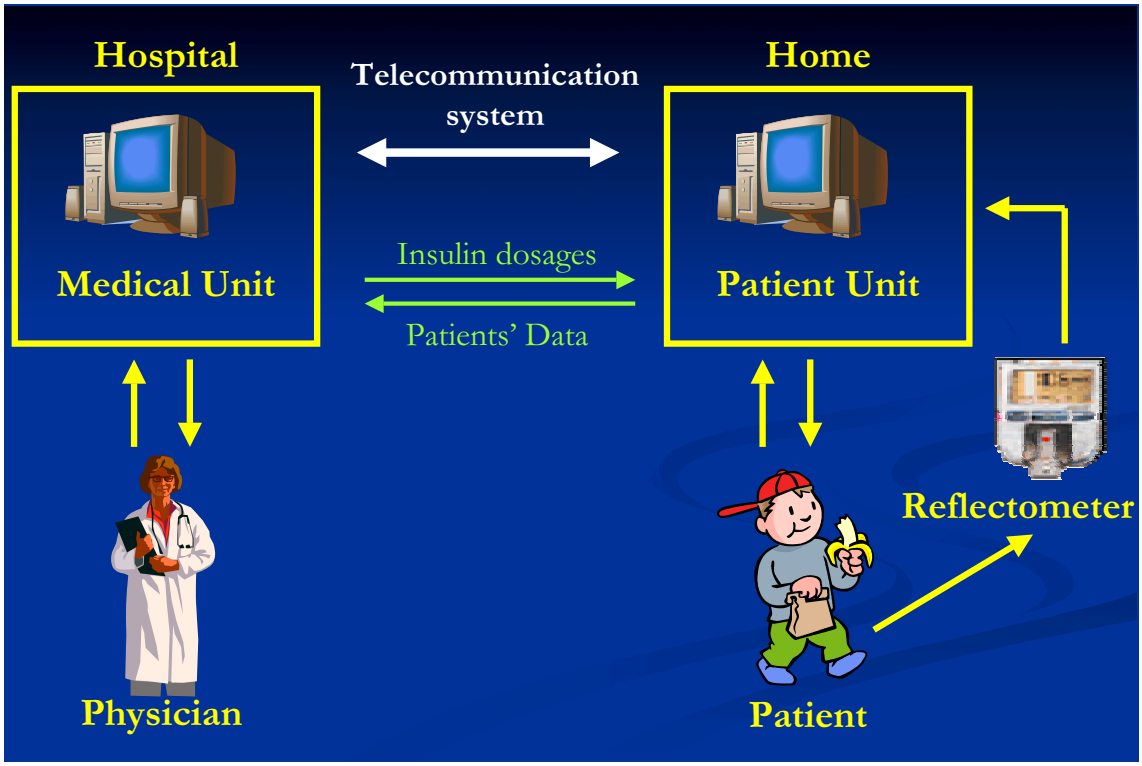
AIMS FOR PATIENTS

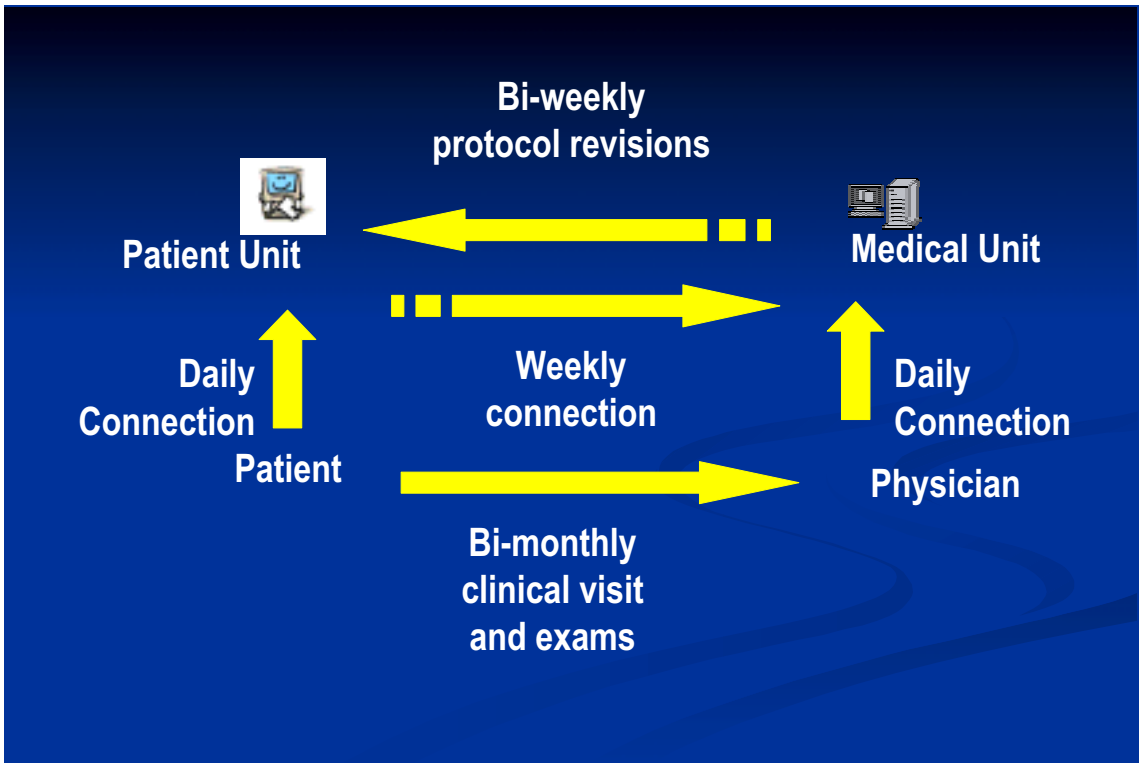
- to be involved more actively in diabetes management through a continuous link with the hospital
- to achieve a higher awareness about the usefulness of a better metabolic control as well as a higher level of education
- to self-adjust insulin dosages within the limits established by the physician

T-IDDM PROJECT

The European Community sponsored project T-IDDM (Telematic management of IDDM), a telemedicine service through a careful analysis of current medical practice, started in 1999 at Pediatric Diabetic Unit in Pavia.

The system is based on 2 main components: Patient Unit (PU), Medical Unit (MU) connected by a telecommunication system .




Bi-weekly
protocol revisions
Patient Unit
Medical Unit
Daily
Connection
Patient
Weekly
connection
Daily
Connection
Physician
Bi-monthly
clinical visit
and exams


Varazze Camp 2003

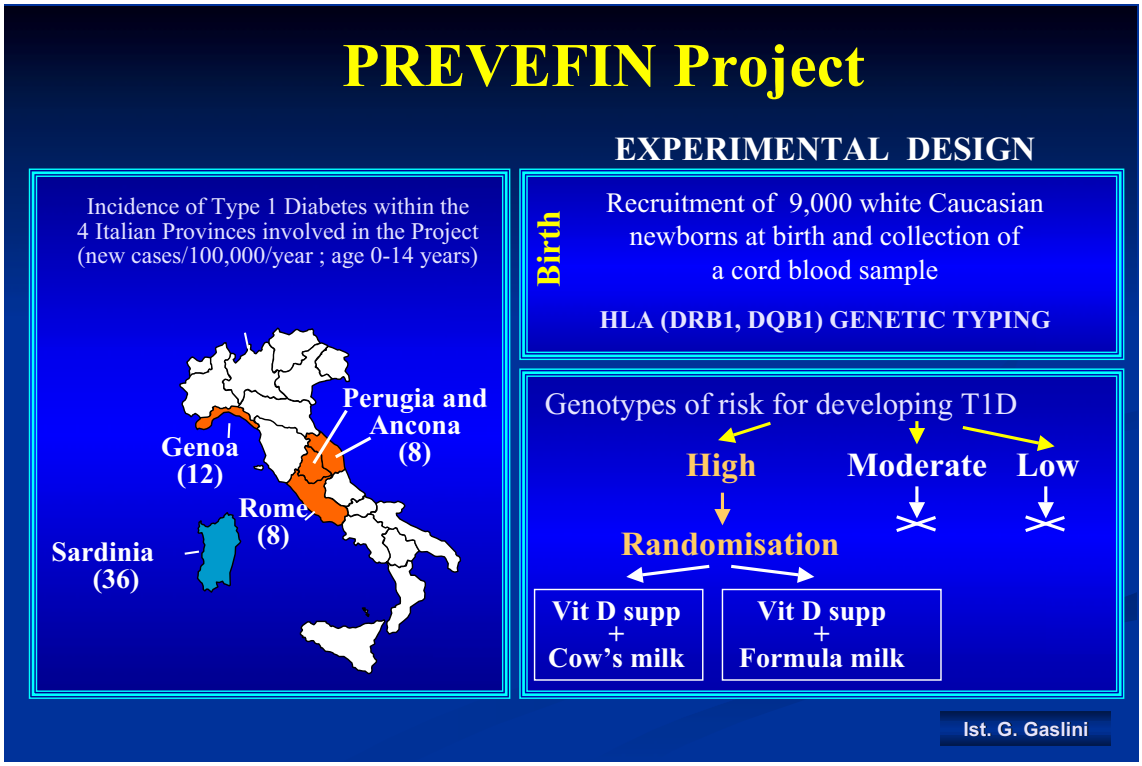
Varazze Camp 2003

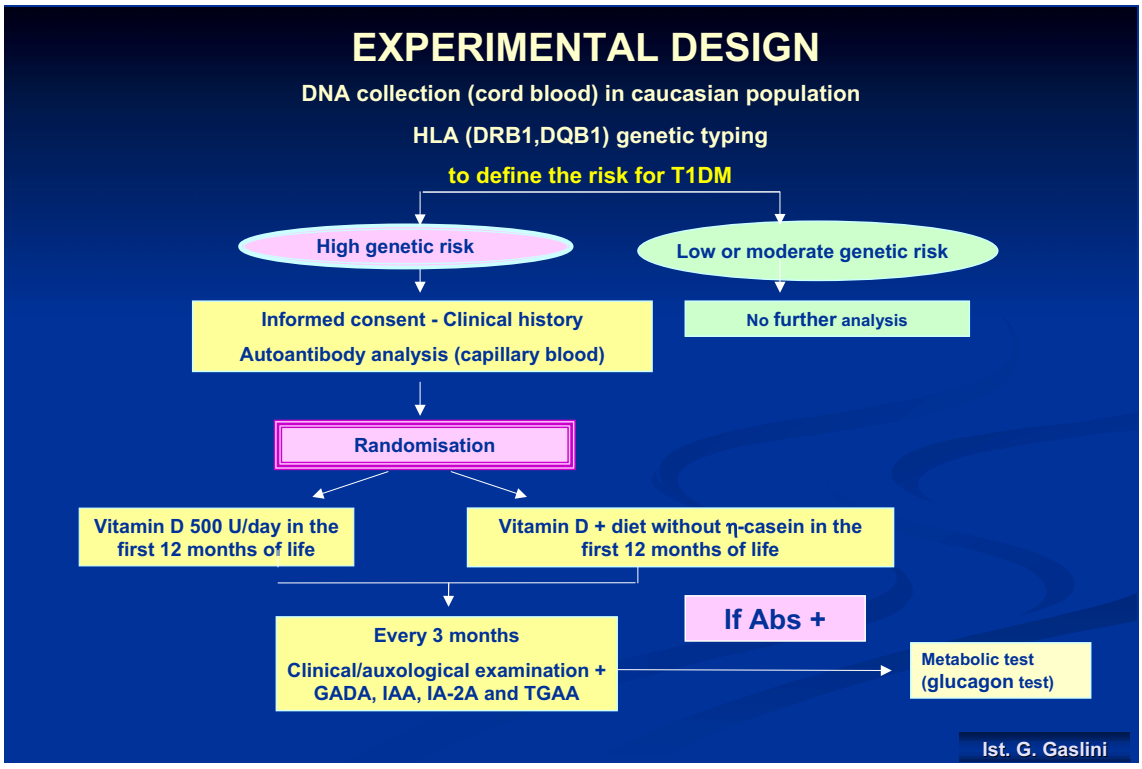
Table I. Strategies for stopping the development of type I diabetes.

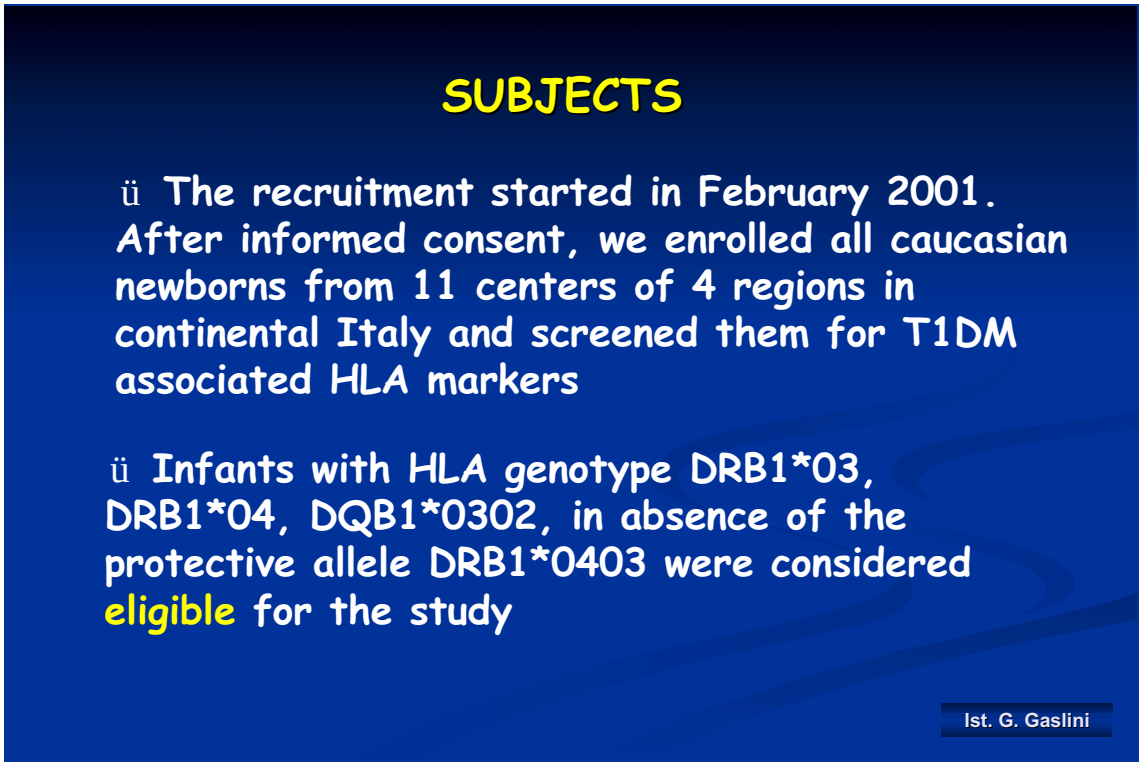
Type of prevention	Disease stage	Strategies	Markers
Primary	Genetic predisposition	Avoid environmental triggers	Genes
Secondary	Subclinical disease process	Prevent, arrest or delay beta cell destruction	Antibodies Pancreatic hormones
Tertiary	Clinical disease	Preserve residual beta cell mass Restore or increase beta cell mass through cell transplantation	Antibodies Pancreatic hormones

Gorus FK et al, Best Practice


PREVEFIN ITALY
Milan
Umbria Marche
Liguria
Lazio


PREVEFIN Project
EXPERIMENTAL DESIGN
Incidence of Type 1 Diabetes within the 4 Italian Provinces involved in the Project (new cases/100,000/year ; age 0-14 years)
Perugia and Ancona (8)
Genoa (12)
Rome (8)
Sardinia (36)
Birth
Recruitment of 9,000 white Caucasian newborns at birth and collection of a cord blood sample
HLA (DRB1, DQB1) GENETIC TYPING
Genotypes of risk for developing T1D
High
Moderate
Low
Randomisation
Vit D supp + Cow's milk
Vit D supp + Formula milk
Ist. G. Gaslini


EXPERIMENTAL DESIGN
DNA collection (cord blood) in caucasian population
HLA (DRB1,DQB1) genetic typing
to define the risk for T1DM
High genetic risk
Low or moderate genetic risk
Informed consent - Clinical history
Autoantibody analysis (capillary blood)
No further analysis
Randomisation
Vitamin D 500 U/day in the first 12 months of life
Vitamin D + diet without η-casein in the first 12 months of life
Every 3 months
Clinical/auxological examination + GADA, IAA, IA-2A and TGAA
If Abs +
Metabolic test (glucagon test)
Ist. G. Gaslini


SUBJECTS
ü The recruitment started in February 2001. After informed consent, we enrolled all caucasian newborns from 11 centers of 4 regions in continental Italy and screened them for T1DM associated HLA markers
ü Infants with HLA genotype DRB1*03, DRB1*04, DQB1*0302, in absence of the protective allele DRB1*0403 were considered eligible for the study
Ist. G. Gaslini

RESULTS

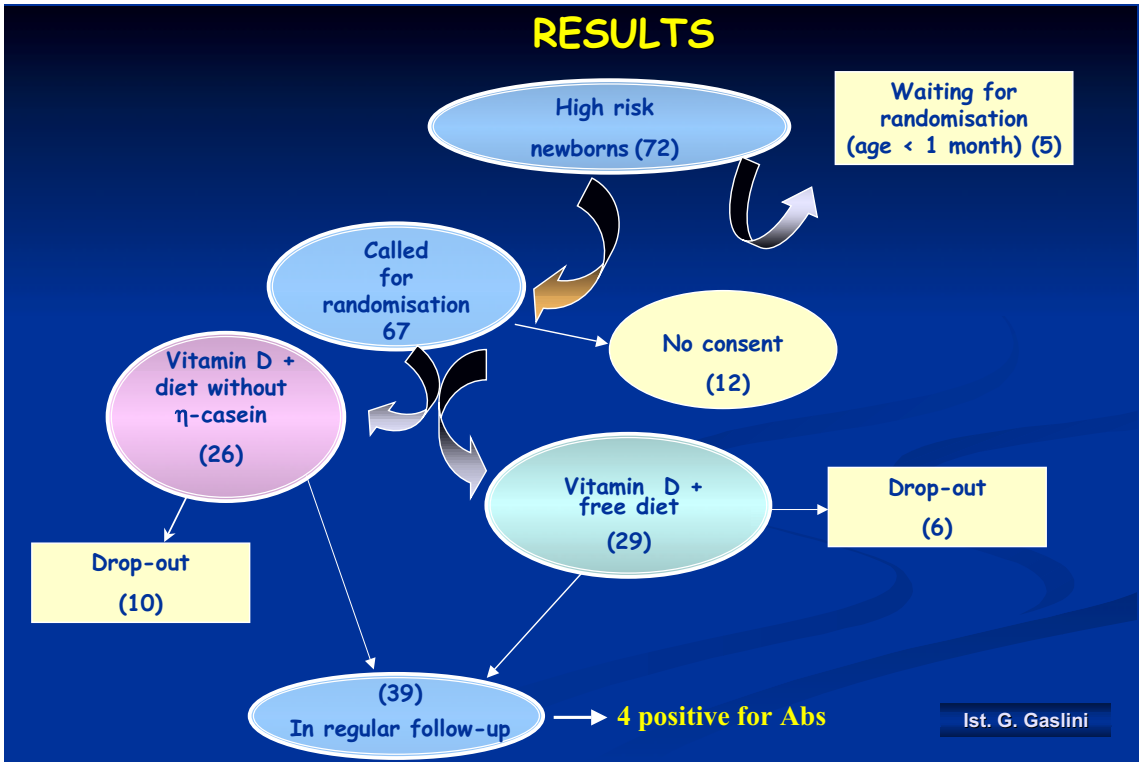
HLA ANALYSIS

HLA	N°	
HIGH RISK*	72	* = 0,8%
INTERMEDIATE RISK	1192	
LOW RISK	8094	
TOTAL	9358	

The expected prevalence of high risk genotype in the Italian population is 1,5 – 2%.

Ist. G. Gaslini

RESULTS



III. OTHER SPECIFIC TYPES

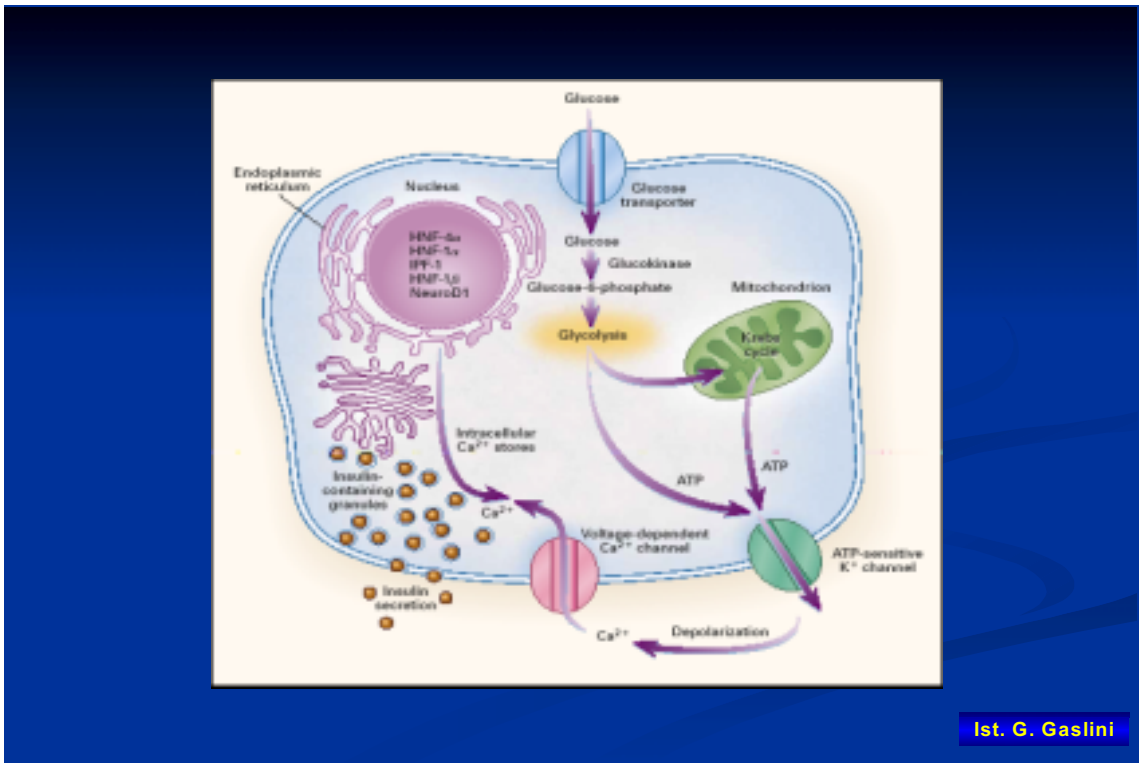
A. Genetic defects of η-cell
(MODY, Mitochondrial diabetes, others)
B. Genetic defects of insulin action
C. Disorders of exocrine pancreas
(cystic fibrosis, others)
D. Endocrinopathies
E. drugs
F. infections
G. Not common forms of diabetes immunomediated
H. Genetic Syndroms associated to diabetes

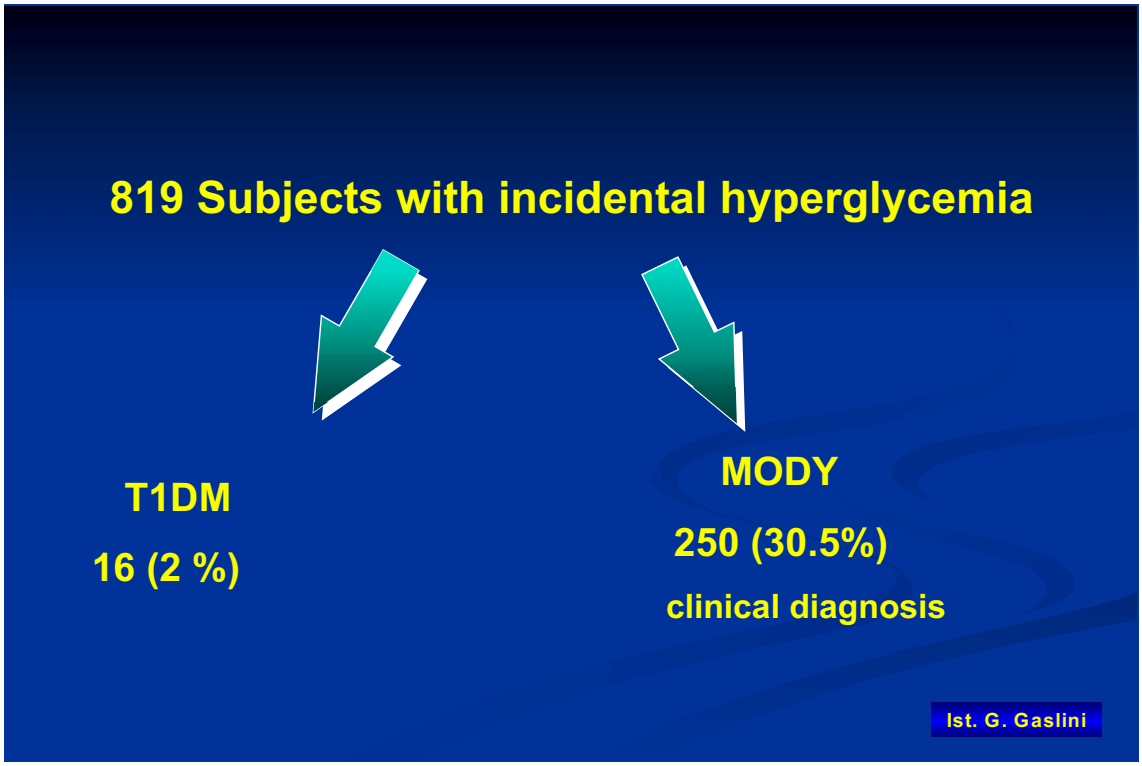
MODY

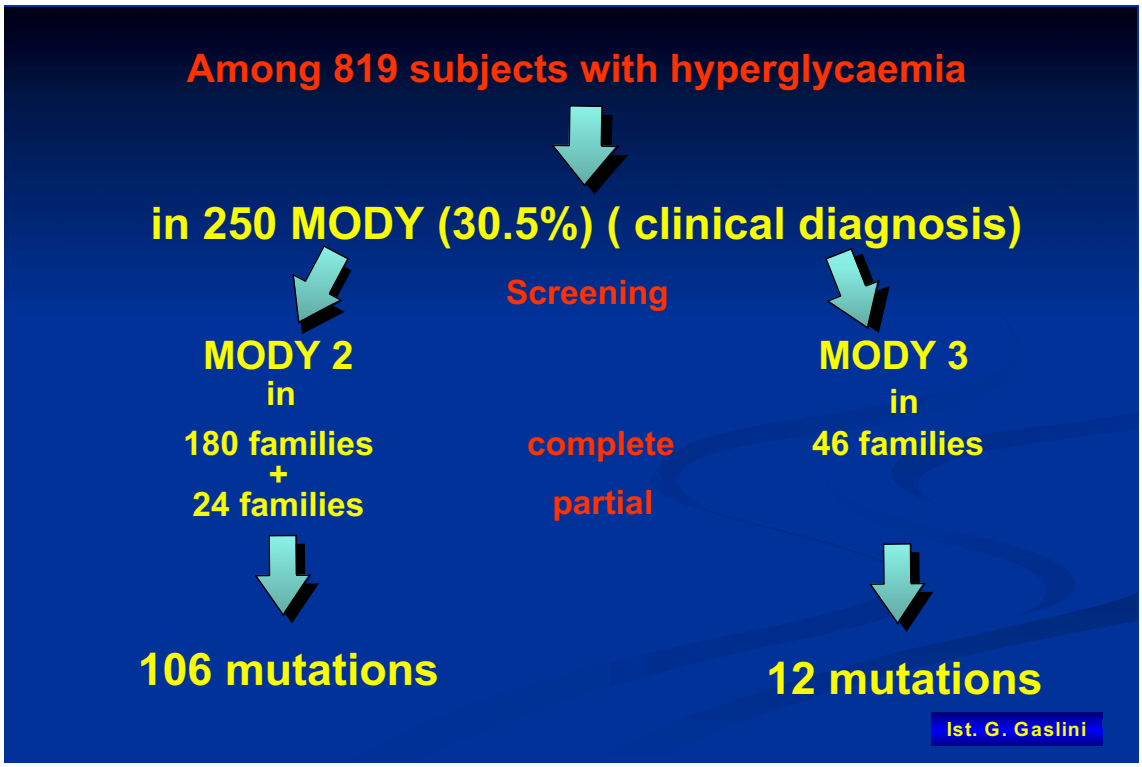
(Maturity Onset Diabetes of the Young)

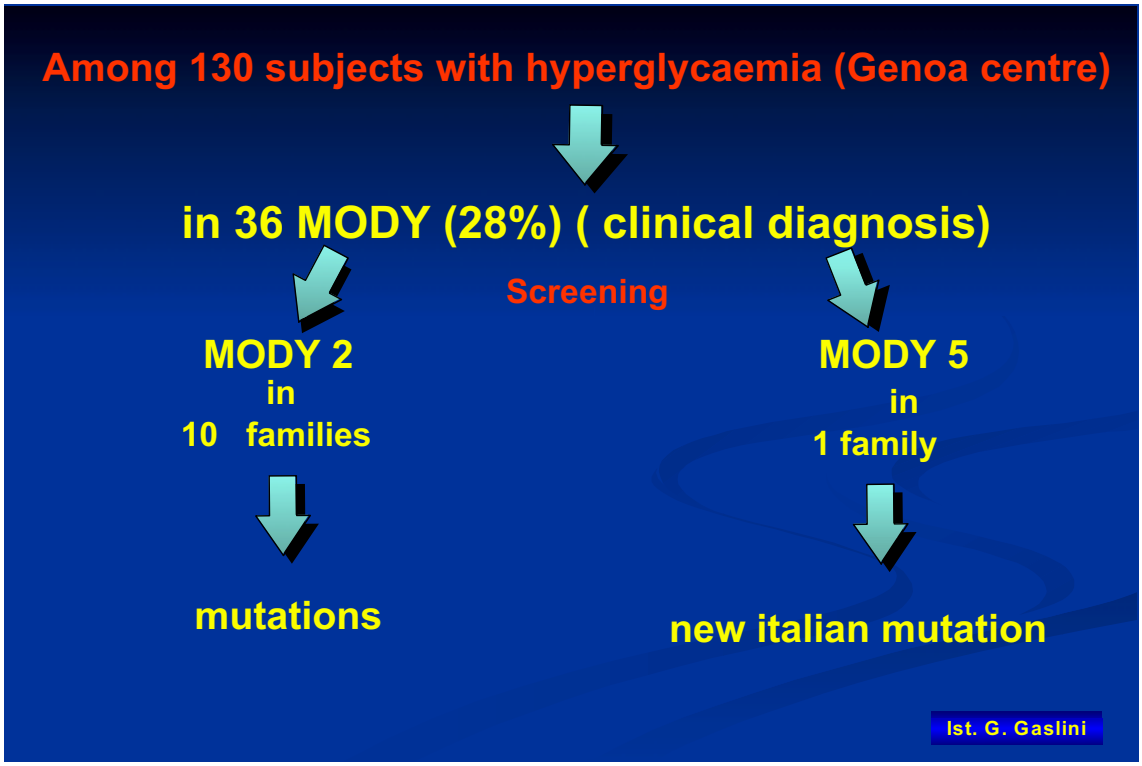
Onset in childhood or young adulthood
Autosomal Dominant Inheritance

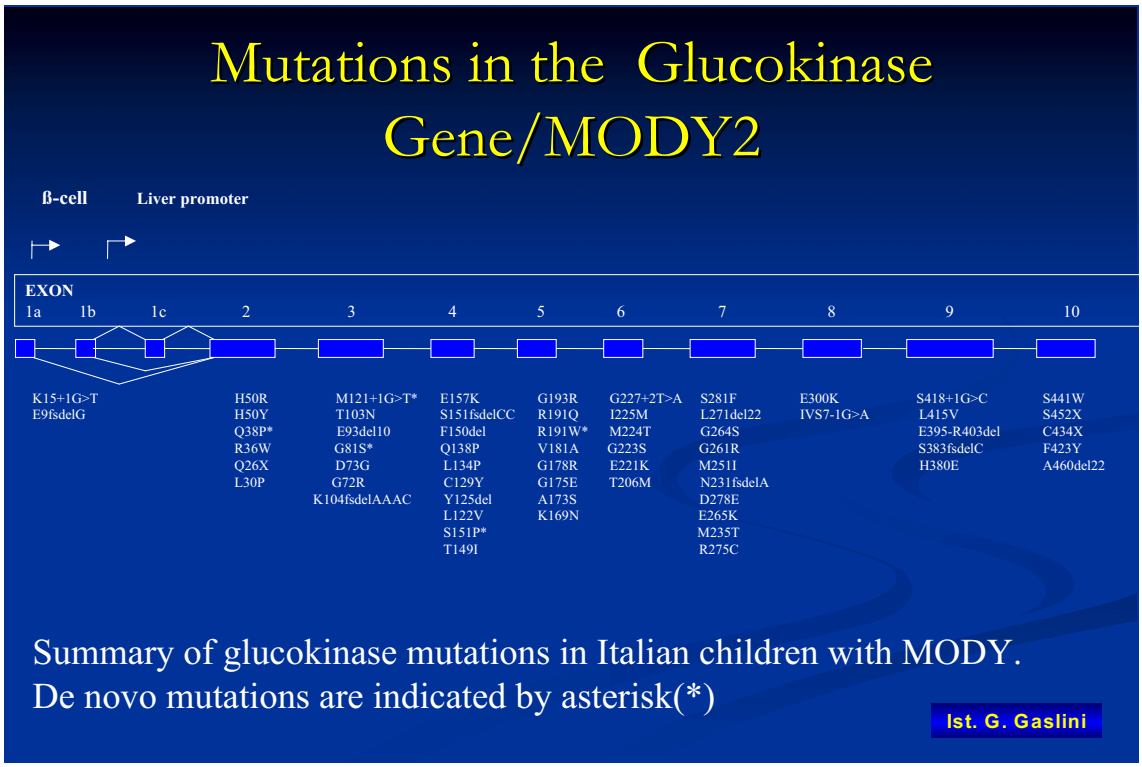
- MODY1 gene: HNF-4ζ
- MODY2 gene: GCK
- MODY3 gene: HNF-1ζ
- MODY4 gene: IPF-1
- MODY5 gene: HNF-1η
- MODY6 gene: BETA2 / NeuroD

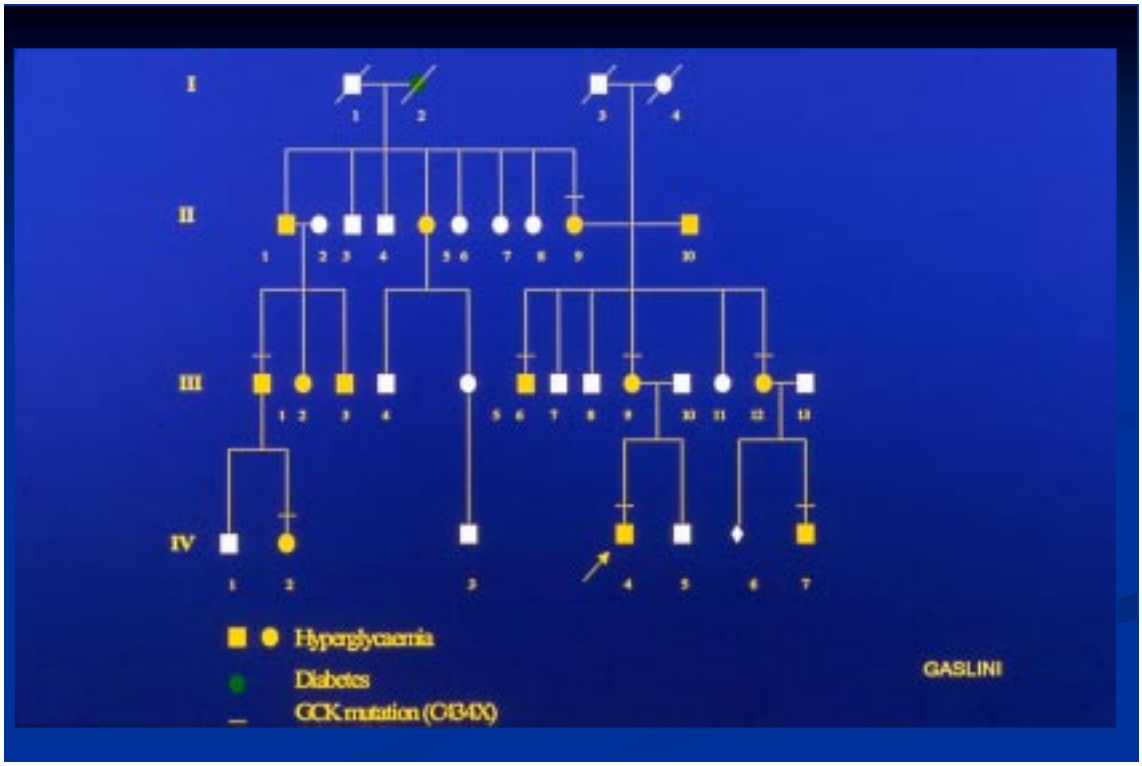

Glucose
Endoplasmic reticulum
Nucleus
Glucose transporter
Glucose
Glucokinase
Glucose-6-phosphate
Mitochondrion
Glycolysis
Krebs cycle
Intracellular Ca2+ stores
Insulin-containing granules
ATP
ATP
Ca2+
Voltage-dependent Ca2+ channel
ATP-sensitive K+ channel
Insulin secretion
Ca2+
Depolarization
Ist. G. Gaslini


819 Subjects with incidental hyperglycemia
T1DM
16 (2 %)
MODY
250 (30.5%)
clinical diagnosis
Ist. G. Gaslini

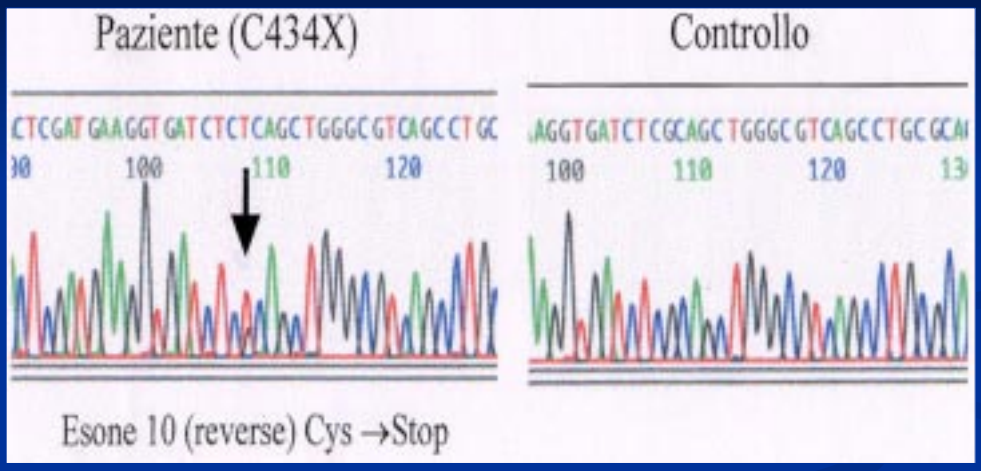

Among 819 subjects with hyperglycaemia
in 250 MODY (30.5%) (clinical diagnosis)
Screening
MODY 2
in
180 families
+
24 families
MODY 3
in
46 families
complete
partial
106 mutations
12 mutations
Ist. G. Gaslini


Among 130 subjects with hyperglycaemia (Genoa centre)
in 36 MODY (28%) (clinical diagnosis)
Screening
MODY 2
in
10 families
MODY 5
in
1 family
mutations
new italian mutation
Ist. G. Gaslini


Mutations in the Glucokinase Gene/MODY2
ß-cell
Liver promoter
EXON
1a 1b 1c 2 3 4 5 6 7 8 9 10
K15+1G>T
E9fsdelG
H50R
H50Y
Q38P*
R36W
Q26X
L30P
M121+1G>T*
T103N
E93del10
G81S*
D73G
G72R
K104fsdelAAAC
E157K
S151fsdelCC
F150del
Q138P
L134P
C129Y
Y125del
L122V
S151P*
T149I
G193R
R191Q
R191W*
V181A
G178R
G175E
A173S
K169N
G227+2T>A
I225M
M224T
G223S
E221K
T206M
S281F
L271del22
G264S
G261R
M251I
N231fsdelA
D278E
E265K
M235T
R275C
E300K
IVS7-1G>A
S418+1G>C
L415V
E395-R403del
S383fsdelC
H380E
S441W
S452X
C434X
F423Y
A460del22
Summary of glucokinase mutations in Italian children with MODY.
De novo mutations are indicated by asterisk(*)
Ist. G. Gaslini


I
II
III
IV
Hyperglycaemia
Diabetes
GCK mutation (C134X)
GASLINI

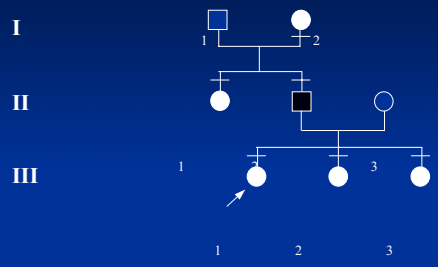
MODY 2 STOP CODON MUTATION UGA



MODY5

Locus	17q
Gene	HNF –1η
Frequence (% of MODY families)	rare
Hyperglycemia	modest / progressive
Organs	pancreas / kidney/ others?
Age of diagnosis	not defined
Therapy	Diet / insulin
Microvascular Complications	rare

HNF-1 η (MODY 5)

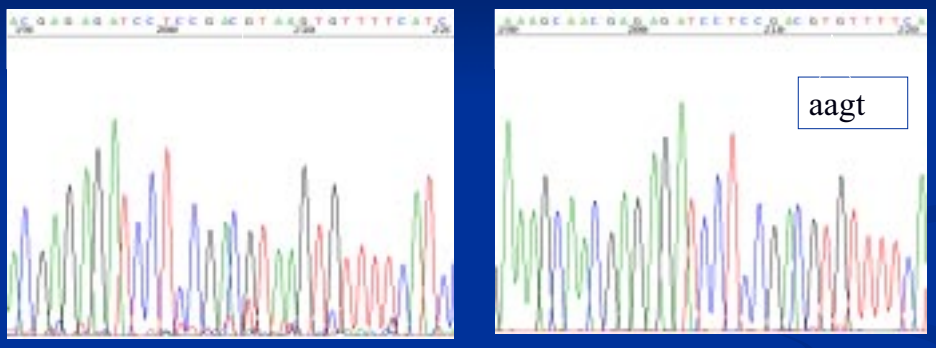


The proband (III-1), with bilateral renal cysts and diabetes diagnosed at 13 years, is indicated by an arrow.
The proband's father (II-2) with horseshoe kidney and diabetes diagnosed at 20 years is represented by a grey square.

- **Heterozygous Mutation HNF-1ß**
- **Horseshoe kidney**
- **Bilateral renal cysts**
- **Displastic kidneys**

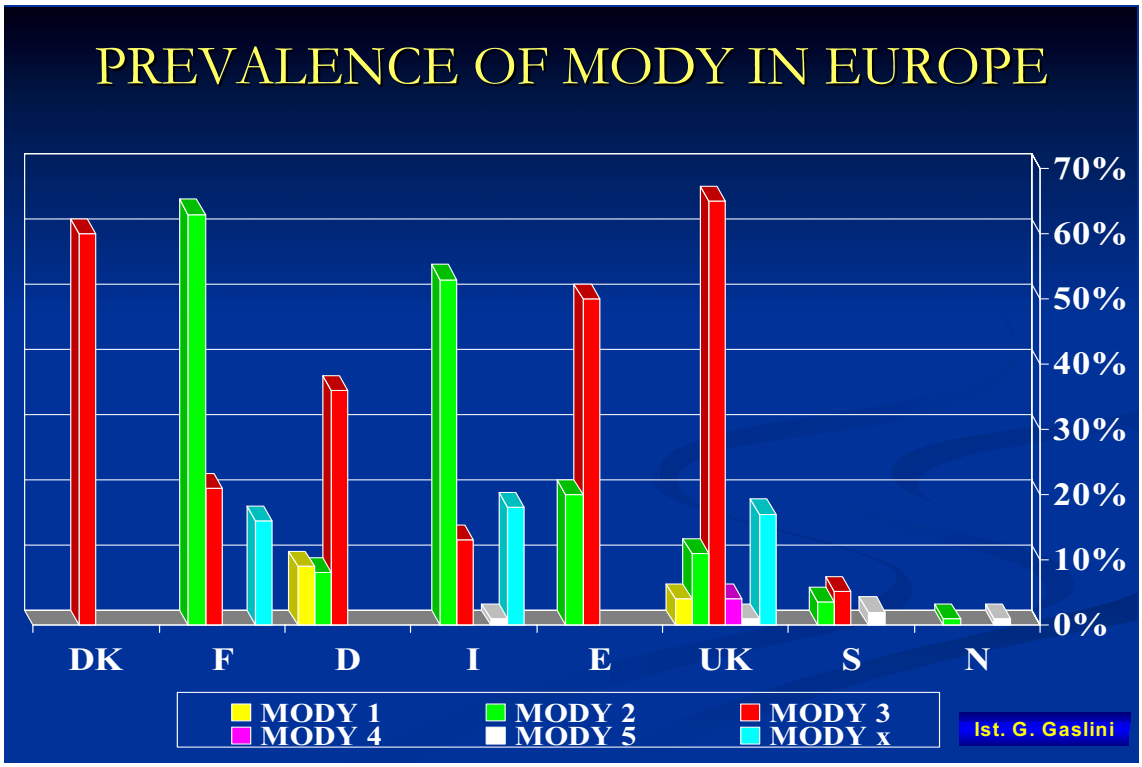
Mutation in the hepatocyte nuclear factor-1 η (MODY-5)

EXON 2 INTRON 2 EXON 2 INTRON 2



Control Patient (IVS2+2delaagt)

I.G.GASLINI



DIFFERENT GENES, DIFFERENT DIABETES

DEFINING OF GENES MUTATION ALLOWS UNDERSTANDING OF CLINICAL HETEROGENEITY OF DIABETES AND GUIDE TO BETTER CLINICAL MANAGEMENT.

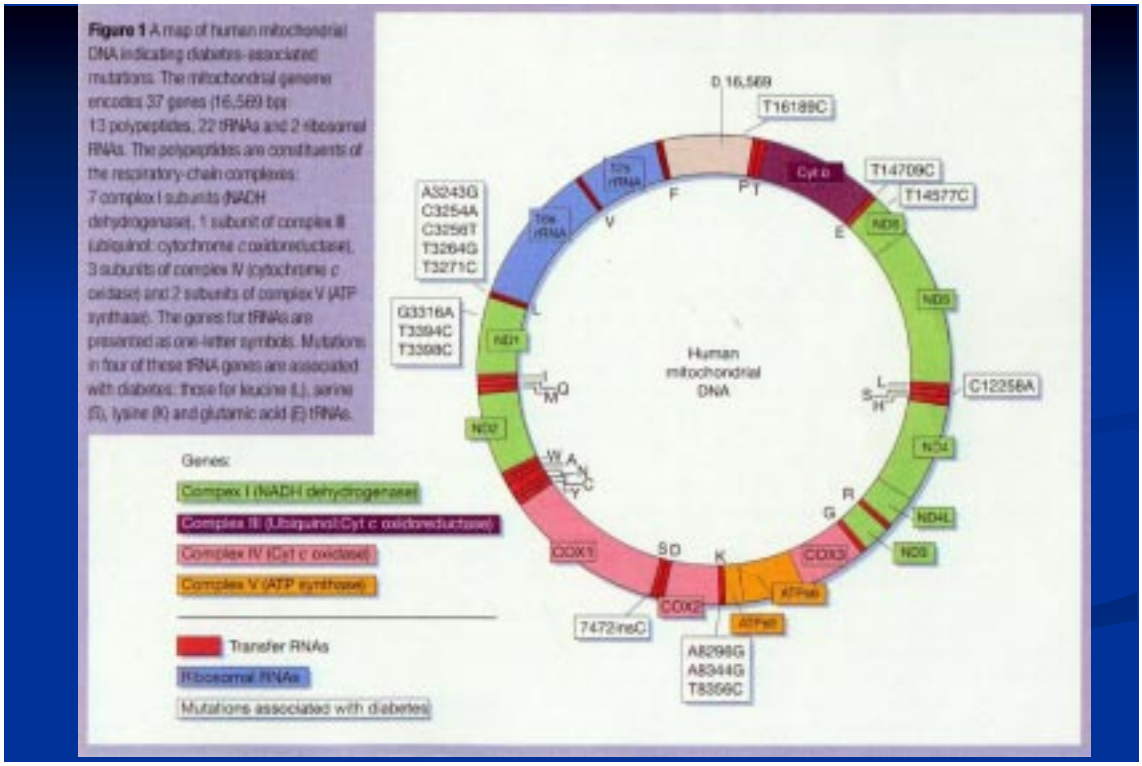
MODY

MODY2 (GCK) stable hyperglycemia, no complication, seldom treatment required.
- maternal MODY increases birth weight
- fetal mutation decreases birth weight

MODY1, 3, 4, 5, 6 have progressive η cell-failure , develop microvascular complications
- range of extra pancreatic phenotype: renal disease and genital development disorders

III. OTHER SPECIFIC TYPES

A. Genetic defects of η-cell
(MODY, Mitochondrial diabetes, others)
B. Genetic defects of insulin action
C. Disorders of exocrine pancreas
(cystic fibrosis, others)
D. Endocrinopathies
E. drugs
F. infections
G. Not common forms of diabetes immunomediated
H. Genetic Syndroms associated to diabetes



E3

WORKSHOP III

Human Molecular Genetics, 1998, Vol. 7, No. 13 2021–2028

ARTICLE

Diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) caused by mutations in a novel gene (*wolframin*) coding for a predicted transmembrane protein

Tim M. Strom[1], Konstanze Hörtnagel[1], Sabine Hofmann[1,3], Florian Gekeler[1,5], Curt Scharfe[1], Wolfgang Rabl[4], Klaus D. Gerbitz[2,3] and Thomas Meitinger[1,*]

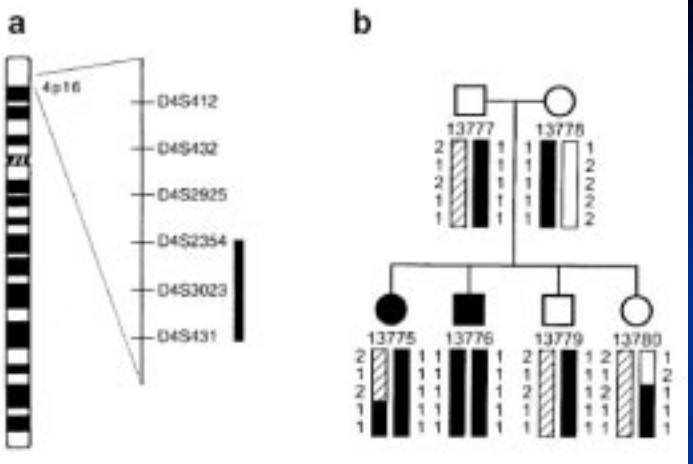


Figure 1. Refined interval for the Wolfram syndrome locus. (**a**) The critical interval in 4p is marked with a bar. (**b**) Chromosome 4p16 haplotypes for family 02 exclude D4S412 and D4S2354 from the critical region assuming that the disease locus in this family was linked to the reported interval between D4S432 and D4S431. Mutation analysis in the *wolframin* gene confirmed that individuals 13779 and 13780 are heterozygous carriers.

Human Molecular Genetics, 1998

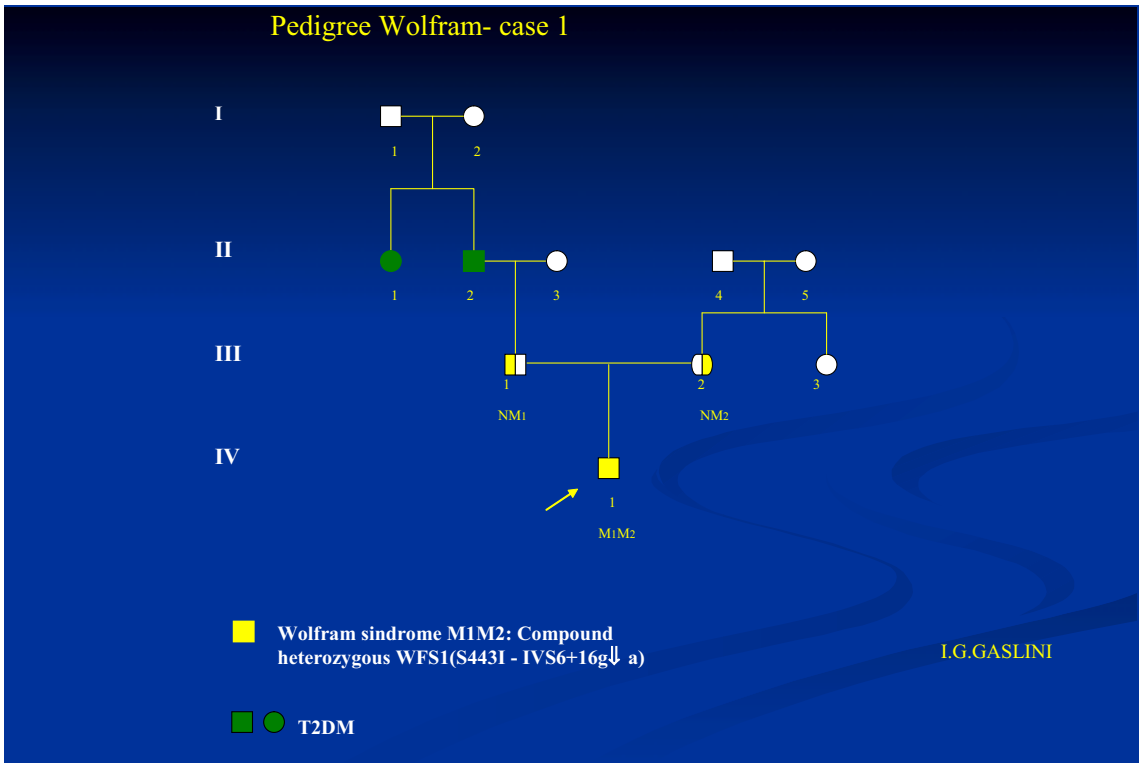
Wolfram Syndrome (WS) is an autosomal recessive neurodegenerative disorder characterized by juvenile-onset diabetes mellitus and progressive optic atrophy, also known by the acronym "DIDMOAD" (Diabetes Insipidus, Diabetes Mellitus, Optic atrophy and Deafness).

Recently different mutations of WFS1 on chromosome 4p16 have been reported in WS patients.

IDENTIFICATION OF NOVEL WFS1 MUTATIONS IN 3 ITALIAN CHILDREN WITH WOLFRAM SYNDROME

.

*Department of Pediatrics and *Neuromuscular Service, University of Genova, G. Gaslini Institute, Genova*


Pedigree Wolfram- case 1
I
II
III
IV
1
2
1
2
3
4
5
1
2
3
NM1
NM2
1
M1M2
Wolfram sindrome M1M2: Compound heterozygous WFS1(S443I - IVS6+16g⇓ a)
I.G.GASLINI
T2DM

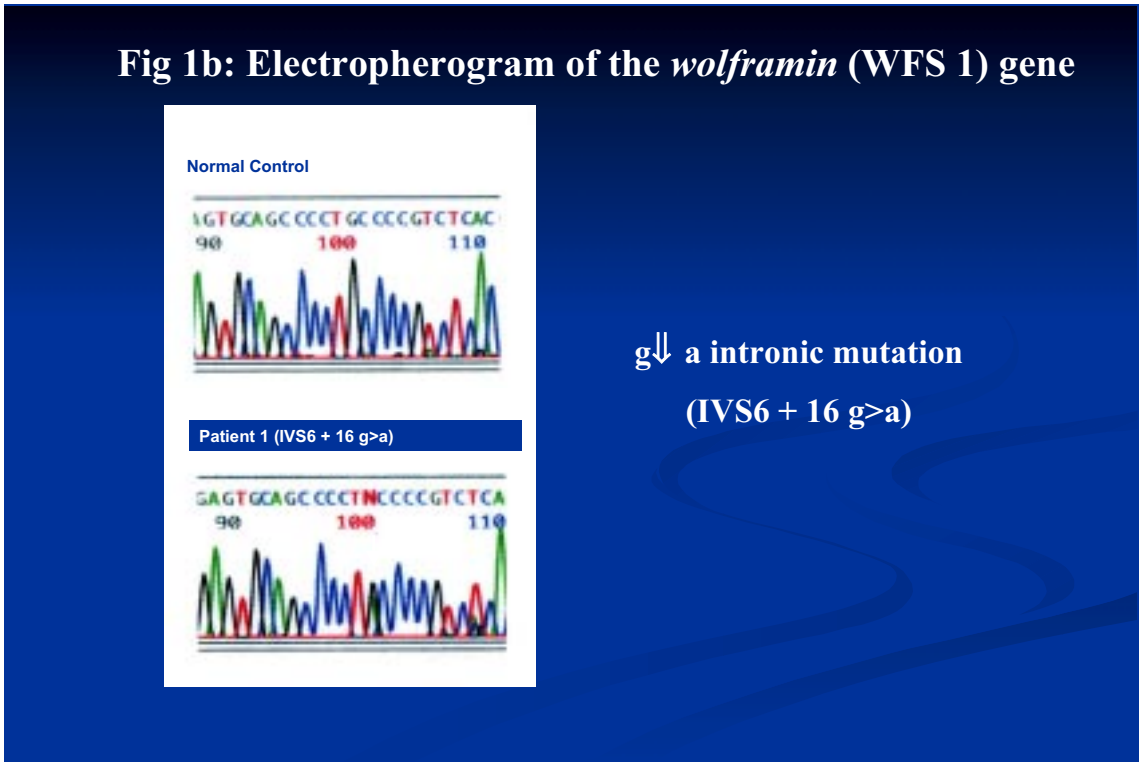
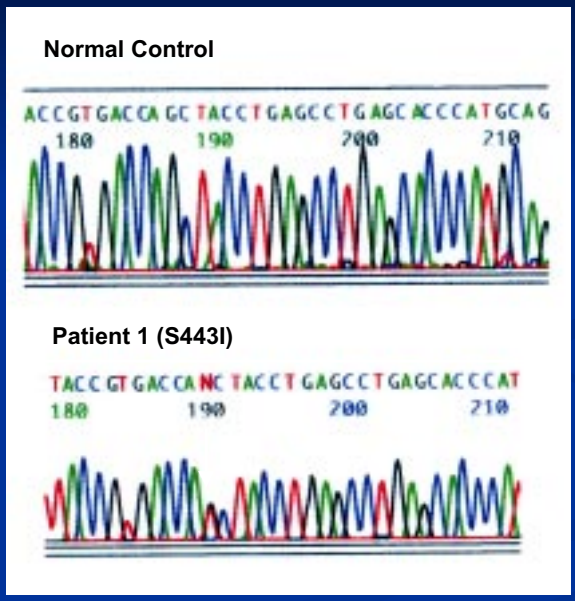


Fig 1b: Electropherogram of the wolframin (WFS 1) gene
Normal Control
Patient 1 (IVS6 + 16 g>a)
g⇓ a intronic mutation
(IVS6 + 16 g>a)

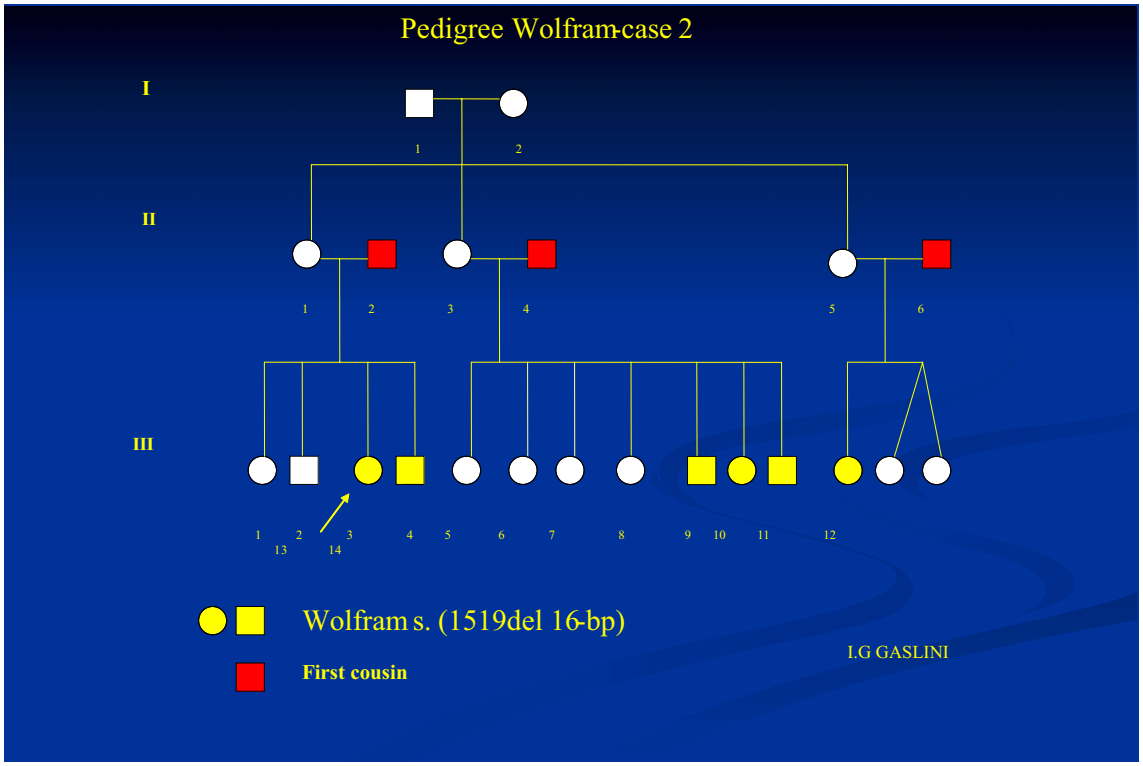
Fig 1a: Electropherogram of the *wolframin* (WFS 1) gene



S443I

G⇓ T nucleotide 1328

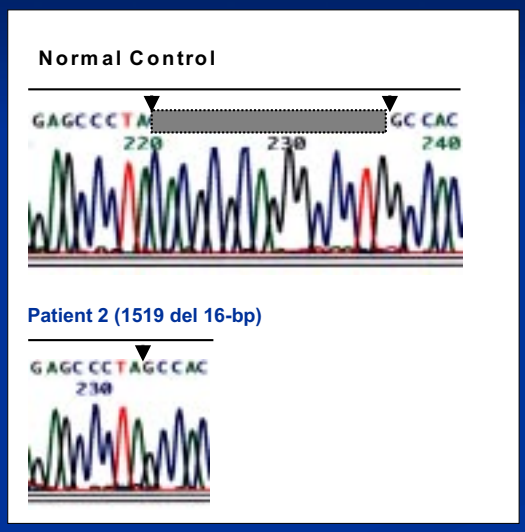
AGC ⇓ ATC
(Ser) (Ile)



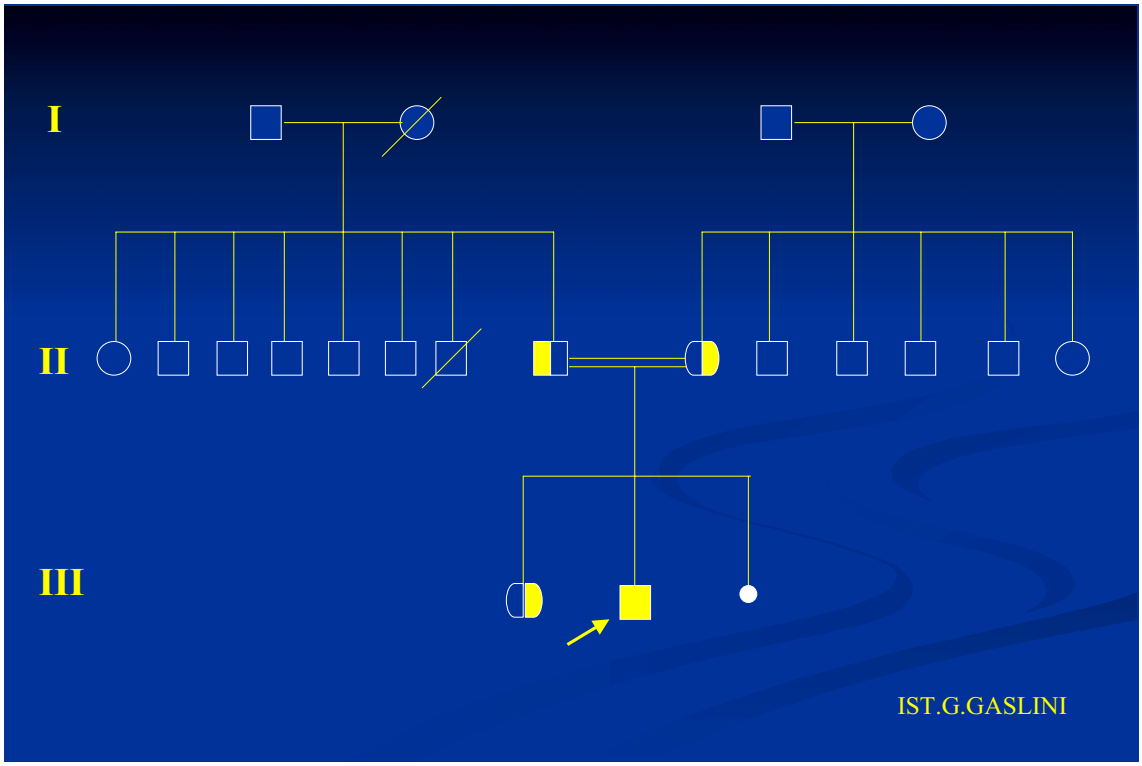
E3

WORKSHOP III

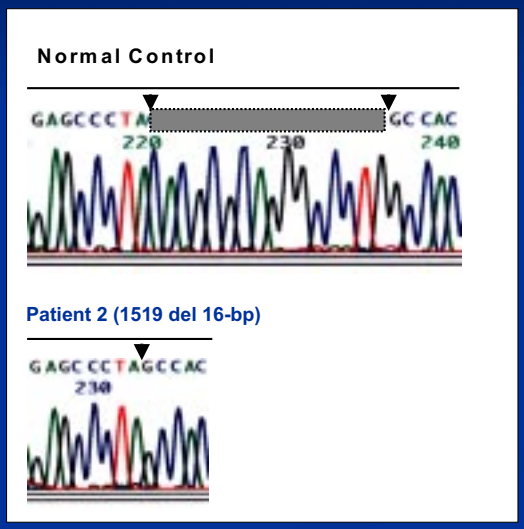
Electropherogram of the *wolframin* (WFS 1) gene in case 2



1519 del 16-bp



Electropherogram of the *wolframin* (WFS 1) gene in case 3



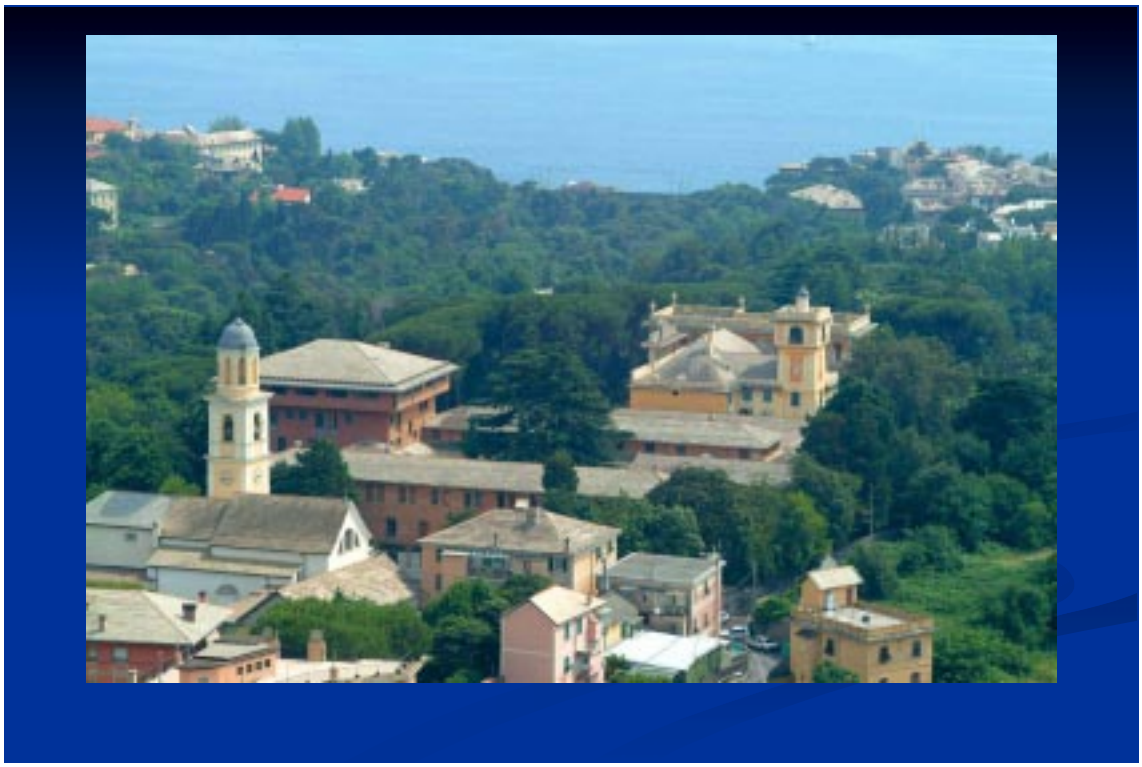
1519 del 16-bp

Age at diagnosis, severity of clinical presentation, and spectrum of WFS1 mutation of Italian Wolfram Syndrome patients

Patient	Age (yrs) /sex	Age at onset of main clinical features	WSF 1 mutations
Case 1	19/m	DM 12 yrs, DEAF 13 yrs, OA 13 yrs	**S443I** (ht-mother); **IVS6+16 g->a** **H611R** (ht – father);
Case 2	15/f	DM 6 yrs, DI 9 yrs, OA 12 yrs	**1519 del 16-bp** (h) **R708 C** (ht)
Case 3	15/m	DM 4 yrs, OA 6 yrs, Resp. Failure 12 yrs	**1519 del 16-bp** (h)

ht: heterozigous mutation; **h: homozigous mutation**

I.G: GASLINI



Meeting	
DATE	**TITLES**
july 17 -18, 2003	Infectious Diseases, Immunology & Clinical Microbiology
september 15 – 26, 2003	Pediatric Surgery
october 13-14, 2003	Advances in the treatment of cerebral palsy
october 20-24, 2003	II course in pediatric kinesiology
october 13-20-27, 2003	Corse in Management

What Gaslini is doing for children with diabetes

- Studying the ***epidemiology*** of T1D 0-14 yrs in Liguria region
- Studying the ***immunologic and genetic markers*** for T1D and other autoimmune diseases (TD and CD) in diabetic children and their first degree relatives
- ***HLA screening*** for T1D at birth in the general population and implementation of a ***primary prevention*** trial with vitamin D and cow's milk hydrolysate
- Trying to improve ***education*** in summer camps and with a telemedicine service in patients with T1D
- Defining of ß-cell genetic defects : ***MODY***, ***Mitochondrial diabetes***
- Defining of genetic syndromes associated to diabetes :***Wolfram syndrome***

Gaslini and the care of diabetic children in the Mediterranean Countries

- Comparing data from Liguria and other Mediterranean countries by new collaborative studies (T1D epidemiology, immunologic and genetic markers for T1D, prevalence of others autoimmune diseases …)
- Collaborative studies on prevalence of ß-cell genetic defects (*MODY, Mitochondrial diabetes)* and genetic syndromes associated to diabetes (*Wolfram syndrome)*
- Trying to improve *education* in international summer camps and with a telemedicine service in patients with T1D
- *International School* for Doctors and Paediatric Nurses in the old Villa Quartara in Castagna
- *Sensitizing European Health Autorities & population* towards care for diabetic children
- *Improving* the current care of diabetic children in the Mediterranean

Gaslini and the care of diabetic children in the Mediterranean Countries

Renata Lorini
Pediatric Clinic-University of Genoa-G.Gaslini Institute, Genoa, Italy

In the first slide we can see the Giannina Gaslini Institute founded by Gerolamo Gaslini in 1931. Gaslini Institute is a general paediatric research hospital for the treatment of all children with no discrimination in terms of culture, religion or nationality. In building 16 of the Gaslini Institute there is the Regional Reference Pediatric Center for Diabetology.
Globally diabetes is a disease in evolution.These global changes in diabetes are also affecting children and adolescents, and the incidence of all types of diabetes is rising.
As we know, Type 1 diabetes is one of the most serious and frequent chronic diseases in children with increasing incidence rate in many parts of the world.
The 4th slide shows the evolution of diabetes mellitus, namely an increased incidence of type 1 diabetes, with an early peak in under 5-year-old children and progression into adulthood, and an even higher incidence of type 2 diabetes , with extension into adolescence and childhood.
A wide variation of type 1 diabetes mellitus (T1DM) incidence has been demonstrated in Italy.In order to assess the present incidence of type 1 diabetes in 0 to 14-year-old children in Liguria, newly diagnosed cases were identified prospectively from 1989 to 1998. During 10 full calendar years 219 new cases of T1DM in children were diagnosed in Liguria.
In the slides, we can see the distribution by year and by age at diagnosis of T1DM in Liguria region. The standardized incidence rate over the 10-year period was 12.56 cases per 100.000 per year. The age-specific incidence rate was higher in the 10 to 14-year-old age group than in the 0 to 4-year-old age group and in the 5 to 9-year-old age group. These data confirm that the incidence rate in Liguria region is among the highest in Southern Europe and in the Mediterranean regions, excluding Sardinia.
In all our patients the presence at diagnosis of islet cell autoantibodies was determined by radiobinding assay. IAA and/or GADA and/or IA-2A were present in most of our patients and in particular in patients over 12 years of age, as reported in the slide.
We also performed the analysis of HLA-DQA1 and HLA-DQB1 polymorphisms at genomic levels by the polymerase chain reaction/sequence-specific primers technique. Regarding DQA1and DQB1 typing, four susceptible DQalfa-beta heterodimers were present in 35% of patients and two heterodimers in 45%, as reported in the 9th slide.
As we know children and adolescents with diabetes have an increased risk of developing other autoimmune disorders, in particular coeliac disease and autoimmune thyroid disease. Coeliac disease (CD) occurs in 1-10% of children and adolescents with type 1 diabetes. The prevalence is 10-50 times greater than in the general population and varies according to different geographical regions. Antiendomysial IgA antibody (EMA) is the most specific test together with antitransglutaminase antibodies. These antibodies should be combined with total IgA levels to excluded false-negative results.Jejunal biopsy showing villous atrophy confirms definitive diagnosis.
In our experience we diagnosed CD in 18 out of 265 T1DM patients : 1 before T1DM diagnosis, 6 at T1DM diagnosis and 11 after T1DM diagnosis.
Thyroid autoantibodies, particularly microsomal antibodies, are found in up to 20-30% of young people with T1DM. A palpable or visibile goiter may be present in 10-20% of cases. The majority of young people with a goiter and positive thyroid antibodies have Hashimoto's thyroiditis but most of

them are euthyroid. In our experience we found ATA in 12% of our patients, in particular TPOA in 23%, TGA in 5% , TPOA and TGA in 72%
In the 17th slide, we can see the distribution of thyroid antibodies according to age and sex.
In the next slide we can see the distribution of thyroid antibodies according to disease duration. The 19th slide reports the transverse sonogram section of left lobe showing enlarged gland, diffuse hypoechogenecity with pseudonodularity in a girl wirh T1D and Hashimoto thyroiditis.
We follow our patients according to ISPAD (International Society for Pediatric and Adolescent Diabetes) consensus guidelines 2000. These consensus guidelines are aimed at providing heath care providers with clear guidance in both acute and chronic care. The International Diabetes Federation has warmly endorsed these guidelines.
At diagnosis patient management includes the following (see slide 22):
– hospital admission for ketoacidosis
– insulin therapy
– educational intervention: intensive insulin regimen, self monitoring of the disease, data recording in a log book
– adequate food plan
– regular physical activity

After diagnosis, follow-up includes the following (see slide 23):
– Once-twice monthly examination: blood tests, HbA1c, urinalysis, clinical check-up, auxological examination, dietician, new insulin protocol.

Clinical goals of physicians are the following (see slide 24):
– to provide an effective treatment leading to a good glycemic control (HbA1c < 7.5%)
– to delay the onset and/or slow down the progression of chronic complications
– to achieve a careful balance between insulin therapy, diet and physical activity.

Aims for patients are the following (see slide 25):
– to be involved more actively in diabetes management through a continuous link with the hospital
– to achieve a higher awareness about the usefulness of a better metabolic control as well as a higher level of education
– to self adjust insulin dosages within the limits established by the physician.

The complexity of diabetes care led to the development of the EU funded project Telematic Management of Insulin-Dependent Diabetes Mellitus(T-IDDM), as reported in the 26th slide. The system relies on the integration of two modules, a Patient Unit (PU) and a Medical Unit (MU), able to communicate over the Internet and the Public Switched Telephone Network. Using the PU, patients are allowed to automatically download their monitoring data from the blood glucose monitoring device, and to send them to the hospital database. The MU provides physicians with a set of tools for data visualization,data analysis and decision support, and allow them to send messages and/or therapeutic advice to the patients. The T-IDDM service has been evaluated through the application of a formal methodology, and was used by European patients and physicians for about 18 months. The results obtained show the feasibility of T-IDDM telemedicine service.

For 3 years we have organized summer camps for diabetic children in Varazze, near Genoa, with the collaboration of Varazze sailing school (see slides 29-31).
We know that education in summer camps is very important for patient's self management, problem solving, accuracy of blood glucose self estimation, glyco-metabolic control, psychosocial adaptation, improved quality of life. The main aims of camps for young diabetics include education in self-management, social adaptation, improved self-esteem. "Steering a sailing boat is similar to controlling blood sugar".

Due to the increased incidence of T1DM, the screening of individuals at risk for type 1 diabetes and the identification of a means to prevent type 1 diabetes take on undeniable public health significance. A valid approach for the prediction and prevention of type 1 diabetes might be to define at birth, or at an early age, the population at increased genetic risk by analysing the risk alleles, the subsequent follow-up of cases at risk, and the appropriate implementation and suitable timing of preventive measures.

The PREVEFIN Italian project is an effort to identify subjects at risk for type 1 diabetes eligible to primary preventive intervention .

The PREVEFIN project, coordinated by Gaslini Regional Center for Diabetes, is running in four Italian Centres, namely in Genoa, Perugia, Ancona, and Rome. The incidence of type 1 diabetes in the 0- to 14 year old age group varies as follows: Genoa Province 12 /100,000/year, Perugia, Ancona and Rome Provinces 8 /100,000/year.

The first aim of the project is to screen 9,000 Caucasian newborns. Analysis of genetic susceptibility for type 1 diabetes of newborns is proposed to parents in the first days after delivery. After written consent to genetic testing of cord blood sample drawn at birth, HLA (DRB1,DQB1) genetic typing is analysed in the samples. Type 1 diabetes risk genotypes are classified as high, moderate and low risk. Children with high risk genotype are randomised to vitamin D or vitamin D plus milk formula without beta-casein .

In the 35th slide, we can see the Prevefin project flow- chart.

The first aim is the collection of a cord blood sample in 9,000 Caucasian newborns. Then, HLA alleles are analysed in all samples. At the end of the first month, the newborns resulting at high genetic risk are monitored for autoantibodies, and a written informed consent is obtained from the parents if they want their child to randomized to vitamin D or vitamin D plus milk formula without beta-casein prevention trial. Immunologic and metabolic markers are evaluated during the follow-up.

The Prevefin project started in February 2001. To date , 9358 newborns underwent HLA genetic typing. 72 newborns (0.8) are categorised into the high risk group, 1192 newborns into the moderate risk group and 8094 newborns into the low risk group. A total of 55 families with a baby at high risk gave written informed consent to randomisation: 29 children were randomised to vitamin D prevention trial, 26 to vitamin D plus formula milk without beta-casein. The 16 drop-outs include 10 families of a child receiving vitamin D plus formula milk without beta-casein and 6 families of a child receiving vitamin D plus free diet.

And now I would like to show some data on other types of diabetes (39th slide)

First of all Maturity onset diabetes of the young, MODY. Patients with MODY have a relatively mild, slowly progressive form of diabetes with autosomal dominant transmission. Onset occurs in childhood or young adulthood. Mutations in 6 genes have been shown to cause MODY.

Moreover I would like to underline that among our Italian subjects with incidental hyperglycemia without immunologic and immunogenetic markers of type 1 diabetes we found 250 (30,5%) subjects with clinical diagnosis of MODY.

To date, genetic analysis has been performed in 180 of our subjects with hyperglycemia.

Mutations in glucokinase gene and in HNF-1alfa gene were found in 106 and 12 patients, respectively.

Among 130 subjects followed in our center we found MODY 2 in 10 families and MODY 5 in one.

In the 51th slide we can see the prevalence of MODY in Europe.

Moreover among subjects with incidental hyperglycemia we identified 3 subjects with novel Wolfram syndrome mutation.

Wolfram syndrome is an autosomal recessive neurodegenerative disorder characterized by juvenile-onset diabetes and progressive optic atrophy,also known by the acronym DIDMOAD (Diabetes Insipidus, Diabetes Mellitus Optic Atrophy and Deafness).
Our patients, 2 boys and 1 girl, are reported in the 66th slide.

In the next slides, we can see the old Villa Quartara in Castagna. In this Villa, the International School for Paediatric Sciences has organized Courses for doctors from the Mediterrean area.

In conclusion
What Gaslini is doing for children with diabetes (see slide 73):
- Studying the epidemiology of T1D 0-14 yrs in Liguria region
- Studying the immunologic and genetic markers for T1D and other autoimmune diseases (TD and CD) in diabetic children and their first degree relatives
- HLA screening for T1D at birth in the general population and implementation of a primary prevention trial with vitamin D and cow's milk hydrolysate
- Trying to improve education in summer camps and with a telemedicine service in patients with T1D
- Defining of ß-cell genetic defects: MODY, Mitochondrial diabetes
- Defining of genetic syndromes associated to diabetes: Wolfram syndrome

About Gaslini and the care of diabetic children in the Meditteranean Countries (see slide 74):
- Comparing data from Liguria and other Mediterranean countries by new collaborative studies (T1D epidemiology, immunologic and genetic markers for T1D, prevalence of others autoimmune diseases …)
- Collaborative studies on prevalence of ß-cell genetic defects (MODY, Mitochondrial diabetes) and genetic syndromes associated to diabetes (Wolfram syndrome)
- Trying to improve education in international summer camps and with a telemedicine service in patients with T1D
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As pediatric diabetes specialists, we believe that the needs of children and adolescents with diabetes and their families are very special and different from those of adults.
We hope this workshop will stimulate each country to develop appropriate standards of care for childhood and adolescent diabetes to obtain an improved delivery of care.

METABOLIC CONTROL IN SIBERIAN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS

Irina Osokina*, Elena Krukova, Valery Manchouk
Institute for Medical Studies of the North, Krasnoyarsk, Russia

Backgraund. Long-term blood glucose control is important to prevent severe late complications. The present status of paediatric diabetes care was not known in Siberia.
The aim was to study diabetes control, management and the prevalence of complications in children and adolescents with diabetes type 1 in Krasnoyarsk region.
Objectives and methods: 94 patients (46 boys/48 girls, mean age 12.3 $\pm$ 2.8 yrs, mean diabetes duration 5,7$\pm$ 1.4 yrs) were examined. Clinical data were obtained by patients interview, reviewing medical records and physical examination. The majority of the patients (96%) received multiple daily insilin injections. The measurement of HbA1c (Bio-Rad) was standartized. All of the patients had been screened for retinopathy and microalbuminuria according to the ISPAD Consensus Guidlines.
Results. Mean HbA1c was 12.3%. 88% of the patients had HbA1c > 10%. The poor metabolic control was associated with the early development of diabetes complications (found in 74% of the patients). The growth retardation had 15.6%. The Moriac's syndrome (the growth and puberty retardation, gepatomegalia) was diagnosed in 12% patients. The prevalence of microalbuminuria was 12 % (the mean duration of diabetes was 8.1±1.5 years, the average HbA1c level 12.8±0.6%). In one patient was determined proteinuria (487 mg/day). Non-proliferative retinopathy was diagnosed in 24% of diabetic patients (the mean duration of diabetes was 5.7±0.3 years). One was blind and 2 had proliferative retinopathy. In children with duration of diabetes 5-10 years the frequency of the diabetic retinopathy was 33%, more than 10 years - in 50% of the patients. The diabetic cataract was diagnosed in 4 patients. Out of 94 paediatric patients, 31 (33%) had limited joint mobility. The diabetic neuropathy was diagnosed in 16% of the patients (the mean duration of diabetes was 5.5±0.2 years, the average HbA1c level was 14.5±4.3%). 4 patients (4.2%) had necrobiosis lipoidica diabeticorum.
Conclusion. This study shows low quality the management of children and adolescents with diabetes in Siberia. Optimization diabetes care system and strengthening of diabetes education in the future may be beneficial in improving the present state.

SUSTAINING COMPREHENSIVE HEALTH CARE FOR DIABETIC CHILDREN IN MOROCCO

A.Balafrej , B.Benhammou , N.Bennani , N.Bencherifa , A.Touzani
Children's Hospital , Rabat , Morocco

Summary

Type 1 Diabetes concerns approximately 10,000 Moroccan children below 15 years. When lacking of appropriate care, these children are subject to iterative hospitalisations and, in the long term, to handicapping degenerative complications. Appropriate care involves information and training of the patients, as well as material and psychological support to their families. To reduce the frequency of these complications, an outpatient clinic for diabetic children was created in 1986 at the Rabat Children's hospital, gathering 800 young diabetics in 2003. In addition to clinical monitoring, a team composed of a variety of different care providers and specialists provides a continuous training program to the diabetic children and their families according to a standardized protocol. The project was made possible through an informal partnership with a parents' association and by a sponsor from the private sector.
Further study is required to generalize this experience based on a quality approach, as well as on equity and efficiency principles, involving the Ministry of Health structures as well as all the other economical and social stakeholders. Beyond diabetes, this approach might be used to monitor other chronic diseases.

Key words: Diabetes, child, Morocco, therapeutic education, partnership, indicators.

Table of contents

I. Context

Diabetes is a chronic invalidating disease, leading to degenerative complications, and is the the first cause of acquired blindness in the world, as well as one of the principal etiologies of terminal renal insufficiency.
As a major public health problem, diabetes concerned nearly 160 million people in the world in 2000. Among them, approximately 10% are young children with Type 1 Diabetes, who have a total lack of insulin secretion and are life-dependent on exogenous insulin[8].

In Morocco, according (7) to the Ministry of Health evaluation, 6.6% (about 2 million Moroccans) suffer from Diabetes and approximately 100,000 among them are insulin dependent. Prevalence on children is not yet known with details. If we extrapolate Algerian data (K. Bessaoud study), we can estimate that prevalence was in 1992 about 2.7/10,000 and annual incidence between 5 and 6 out of 100,000.

The glycaemic instability which characterizes type 1 diabetes leads, especially in children, to severe short and long term complications:

- In the short term, it can lead to acute complications (hypoglycaemia or hyperglycaemia with acidosis) if the patient is not well followed up. These complications require urgent hospitalization and are the cause of an important mortality rate although not listed in developing countries.
- In the long term, it leads to degenerative complications the frequency of which increases with poor metabolic control and the duration of the disease. These particularly expensive and invalidating complications concern about the three quarters of young poorly controlled diabetics after 20 years of evolution, excluding young adults from work and compromising their personal and family future.

Type 1 Diabetes treatment depends on daily insulin injections. Only a treatment based on quality allows for a normal life and reduces the frequency of long term complications. This quality means a rigorous injection technique, adapting insulin doses on daily self-monitoring of blood and urine sugar, and a healthy way of life including food discipline.

While in most western countries diabetic people are totally reimbursed for their treatment by health insurance companies, it is not the same case in Morocco. Up to 2002, young diabetics with a health insurance coverage were only reimbursed for insulin. Blood and urine monitoring strips required to adapt doses and maintain normal glycaemia are not refunded and are expensive due to taxes. In order to get three daily blood tests and a urine test (ISPAD recommendations 5), families must pay at least 1,200 DH per month, which is the nearly equivalent of the minimum salary (1,600 DH or 160 $). Devices aiming to make daily care easier are not reimbursed either.

Nevertheless, since the creation in 1995 of a national Diabetes program at the Ministry of Health, diabetes care is becoming more organized in Morocco. At the provincial level, in the rural health centres, where diabetic people are looked after by a general physician or a nurse, busy health professionals cannot dedicate enough time to their patients. Moreover, they do not have appropriate training or teaching techniques, and therefore the service quality is not always ensured. In addition, while child diabetes creates specific problems, there is no specific care for children. In practice, monitoring of diabetic patients at this level means measuring glycaemia and glycosuria on a daily basis, and giving the patient his insulin dose.

At the regional level, the Ministry of Health created Reference Centres starting in 1997, with the goal of establishing a reference Centre in each region. There are currently five regional Centres in Morocco: Kenitra, Errachidia, Tetouan, Beni-Mellal and Fes. All these Centres are equipped with a laboratory for HbA_1c haemoglobin tests and an ophtalmological unit.

II. Methodological approach

Diabetic treatment of children is constraining and requires the provision of information and training to the young diabetics and their families. Information and training allow the diabetic child to become autonomous for daily care. They also allow their families, and more particularly mothers who often are in charge of care at home, to build new capacities. In addition, this daily rigorous treatment requires a psychological and material support to the young diabetic and his family.

The outpatient clinic for diabetic children, created at the Rabat Children's Hospital in 1986, aimed first of all to autonomize the diabetic children and their families, who until then were dependent on Health Centres for their daily insulin injections, but also to reduce the social and medical impact of diabetes.

The initial idea was simple: by informing and training young diabetics and their families, standardizing medical follow-up, and providing a material support to the poorest, we could provide them a normal life. In this outpatient clinic, the approach is quite different from a classical medical follow-up and looks rather like a preventive action. The aim is preventing in the short term acute metabolic complications leading to iterative re-hospitalisations: up to 25 re-hospitalisations for some young diabetics in 1986. Another objective is maintaining a glycaemia rate closest to the normal range to avoid delayed growth (concerning 25% of diabetic children not looked after) and degenerative complications. These invalidating and expensive complications concern about three quarters of young poorly treated diabetics after 20 years of evolution[6].

This type of care is incompatible with individual monitoring and involves different health specialists, not only in endocrinology and dietetics, but also in pedagogy, communication, psychology and social science. Initially composed of a diabetes paediatrician and a nurse, the medical team includes today 4 paediatricians, one biologist, and one nurse. Since a few months, a young dietician has joined the team part-time. A social assistant has been hired since the beginning of 2001. An efficient partnership with other specialists (ophtalmologists, nephrologists) allows for screening of complications.

In order to support and assist the young diabetics and their families, a parents association was created in 1987. The experience developed and continued thanks to regular subsidies provided by a national holding. This experience led to recommendations on diabetic child care which were adopted by consensus during the National Paediatrics Congress (June 1999) and validated by the Ministry of Health[2].

Nevertheless, if "human structures", i.e. professional staff and patients, are there, the lack of a geographical structure adapted to the needs of young diabetics and their families, as well as the lack of a specific status threaten the project sustainability.