Pharmacological Principles Used in Patient Monitoring with Type 2 Diabetes

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This study assessed the medication used in type 2 diabetes treatment, depending on the glycaemia level and set out the oral anti-diabetics which are recommended, in three study stages: admission, hospitalization and discharge. Eighty patients were selected and diagnosed with diabetes mellitus 2 type, who were registered in the diabetes and nutrition diseases department within Sf. Apostol Andrei Galati Hospital. They were subjected to a series of laboratory tests: blood count, glycosylated haemoglobin, glycaemia level. It were established main classes of anti-diabetic drugs outpatient used and the main types of anti-diabetic agents administrated to patients requiring hospitalization, compared to high glycaemia values. It was given also, the medication used to normalize blood glucose levels during hospitalization and also at discharge. The biguanides associated with sulphonylureas drugs did not provide an adequate glycaemia control, so insulin must be combined with Metformin to normalize blood glucose levels as soon as possible. Glycaemia control was improved and the hypoglycaemia risk was reduced regarding obese patient undergoing treatment with insulin, to whom biguanides were administered.

Keywords : diabetes mellitus, oral anti-diabetics, glycaemia, insulin, biguanides

Lifestyle changes provided by Metformin, represent the foundation stones of type 2 diabetes mellitus management. Another group of pharmacological agents types for this disease were discovered [1]. Addition of sulphonylureas to Metformin treatment have targeted, both the resistance to insulin and the insulin deficiency [2]. One of both drugs must consider different therapeutic option with the type 2 diabetes mellitus patients when the glucose levels, initially controlled by the lifestyle and Metformin, began to rise [3]. Most patients require the addition of another therapeutic agent, individually or in combination: with or without insulin within a few months to a few years [4]. The addition of another anti-diabetic drug to insulin might improve the glycaemia control and possibly reduce the necessary insulin dose [5]. A considerable share of patients will eventually require insulin treatment to maintain long-term glycaemia control, either as mono-therapy or in association with oral anti-diabetics [6-7-9].

The therapies using the effects of glucagon-like peptide-1 (GLP-1), stimulates insulin and inhibit the glucagon secretion dependent on glucose [8]. The purpose of the primary diabetes treatment is to reduce glycaemia levels and to substantially decrease the glycosylated haemoglobin synthesis (HbA1c) to levels lower or around 7% [10-12], in order to reduce efficiently, the macro and micro-vascular diabetes-related complications [13-17]. Medication from all available classes, in single-drug or combined therapies, are used by physicians to treat the patients. Treatment for diabetes complications costs double or even triple than for uncomplicated one [18].

The most important classes of oral-antidiabetics are : biguanides, sulphonylureas, alpha glucosidase inhibitors (AGIs), dipeptidyl-peptidase IV (DPP-4) inhibitors, insuline, thiazolidinediones [19].

Biguanides represent an important class of anti-diabetic oral drugs used in diabetes 2 mellitus treatment . Only a few biguanides exert a glucose-lowering effect. As can be seen in figure 1, which indicates the chemical structure of these compounds, the biguanides have a shared basis derived from two linked guanidines chains (blue colored in fig. 1). The pharmacological differences between guanidines are determined by characteristic differences between in their non-polar hydrocycarbon side chains (red colored in fig. 1). As a result of these non-polar side chains, biguanides bind to membrane, phospholipids and other hydrophobic biological structures [20-22].

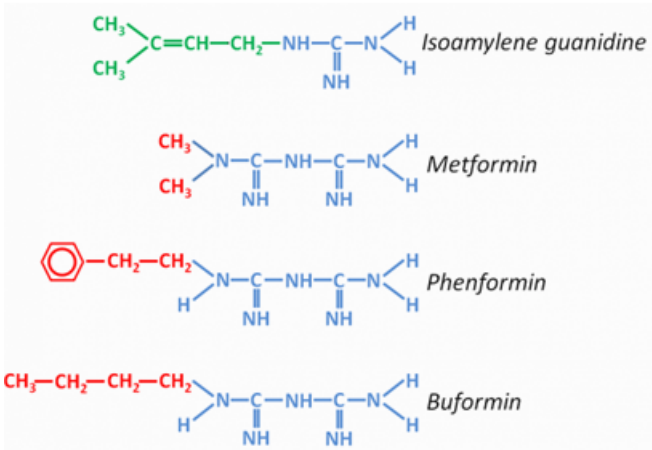

Fig. 1. Chemical structure of Isoamylene guanidine and biguanides including Metformin [20] IUPAC name of Metformin: 1,1-Dimethylbiguanide

It is known that metformin's administration lowers plasma glucose and reduces internal insulin requirement in insulin – treated patients. It is therefore classified as an insulin synthesizer and can be combined with almost any other treatment used for diabetes. Its glucose –lowering effect is primarily due to hepatic gluconeogenesis inhibition and thus of hepatic glucose output, which is increased two-fold or more in type 2 diabetes mellitus. The main effect of this biguanide drug is to acutely decrease hepatic

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glucose production, mostly through a mild and transient inhibition of the mitochondrial respiratory-chain complex . In addition, the resulting decrease in hepatic energy status activates the AMP-activated protein kinase (AMPK or 5' adenosine monophosphate-activated protein kinase), a cellular metabolic sensor, providing a generally accepted mechanism for metformin action on hepatic gluconeogenic program.

The demonstration that respiratory-chain complex , but not AMPK, is the primary target of metformin was recently strengthened by showing that the metabolic effect of the drug is preserved in liver-specific AMPK-deficient mice [22, 23].

A second class of oral anti-diabetics is represented by sulphonylureas drugs. All pharmacological sulfonylureas contain a central S-arylsulfonylurea structure with a *p*-substituent on the phenyl ring (**R^1**) and various groups terminating the urea *N'* end group (**R^2**). Chemically meaning, this functional mechanism can be easily installed by reacting aryl -sulfonamides (R^1—C_6H_4—SO_2NH_2) with isocyanates (R^2—NCO) [24, 25].

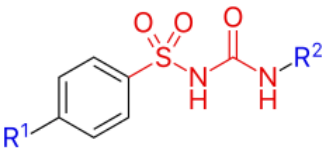

Fig. 2. General chemical structure of a sulphonylurea , showing the backbone of these compound (in red) and its side chains (in blue) [25]

Glimepiride is an oral antidiabetic drug which belongs to the sulfonylurea group and usually is given as an oral anti-diabetic therapy for patients with type 2 diabetes mellitus. Glimepiride acts to lower blood glucose by stimulating the release of insulin from pancreatic β-cells [26].

In figures 3 and 4 shown below are presented chemical structures of Glimepiride and Glubenclamide, two important compunds of sulfonylurea group :

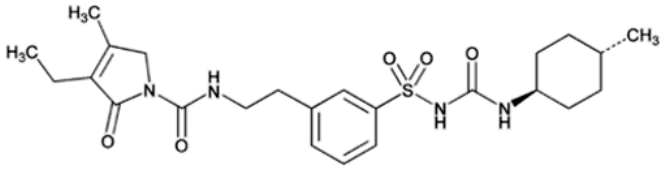

Fig 3. Chemical structure of Glimepiride IUPAC name: 4-ethyl-3-methyl-N-[2-[4-[(4 methylcyclohexyl) carbamoylsulfamoyl] phenyl]ethyl]-5-oxo-2H-pyrrole-1-carboxamide [26]

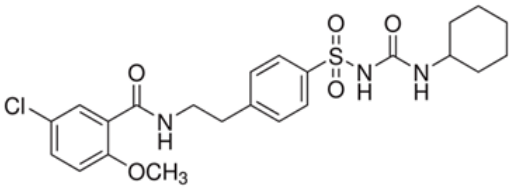

Fig 4. Chemical general structure of Glibenclamide IUPAC name: 5-chloro-N-[2-[4-(cyclohexylcarbamoyl-sulfamoyl)phenyl]ethyl]-2-methoxybenzamide [27]

Sulfonylureas bind to and close ATP-sensitive K^+(K_{ATP}) channels on the cell membrane of pancreatic beta cells, which depolarizes the cell by preventing potassium exit. This depolarization opens voltage-gated Ca^{2+} channels. The rise in intracellular calcium leads to increased fusion of insulin granulae with the cell membrane, and therefore increased secretion of (pro)insulin [28].

There are some evidences that sulfonylurea derivative also sensitize β-cells to glucose, that they limit glucose production in the liver, that they decrease lipolysis (breakdown and release of fatty acids by adipose tissue) and slow down clearance of insulin by the liver [29].

Alpha glucosidase inhibitors (AGIs) are a special class of anti-diabetic drugs, derived and isolated from bacterial cultures or their derivatives (acarbose from *Actinoplanes*, miglitol, a semisynthetic derivative of 1-deoxynojirimycyn, from *Bacillus* and *Streptomyces sp* and voglibose, from *Validamycin A.*, product of *Streptomyces hygroscopicus var limoneus* [30].

Alpha glucosidase inhibitors are drugs that inhibit the absorption of carbohydrates from the gut, thereby controls postprandial hyperglycaemia with unquestioned cardiovascular benefit. They may be used in the treatment of patients with type 2 diabetes or impaired glucose tolerance. Their action consists to considerably reduce postprandial hyperglycemia. Hiperinsulinemia will inevitably increase in time [31, 32].

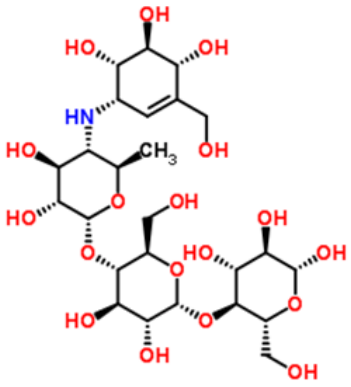

Fig. 5. Chemical structure of Acarbose. IUPAC name: (3R,4R,6R)-5-[(2R,3R,4R,5S,6R)-5-[(2R,3R,4S,5S,6R)-3,4-dihydroxy-6-methyl-5-[[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl) cyclohex-2-en-1-yl]amino]oxan-2-yl]oxy-3,4-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-6-(hydroxymethyl)oxane-2,3,4-triol [33, 34].

Dipeptidyl-peptidase IV (DPP-4) inhibitors inhibit the degradation of the incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). The first available DPP-4 inhibitors are ***sitagliptine*** and ***vildagliptine***. These compounds are orally active and have been shown to be efficacious and well tolerated [35].

Current pharmacologic treatments for type 2 diabetes are based upon increasing insulin availability (either through direct insulin administration or through agents that promote insulin secretion), improving sensitivity to insulin, delaying the delivery and absorption of carbohydrate from the gastrointestinal tract, or increasing urinary glucose excretion. Glucagon-like peptide-1 (GLP-1)-based therapies (eg, dipeptidyl peptidase 4 [DPP-4] inhibitors, GLP-1 receptor agonists) affect glucose control through several mechanisms, including enhancement of glucose-dependent insulin secretion, slowed gastric emptying, and reduction of postprandial glucagon and of food intake [36].

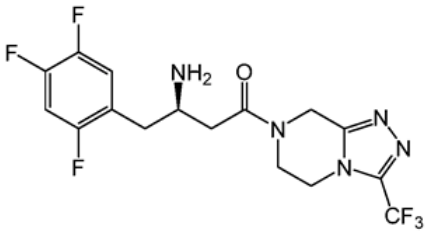

Fig. 6. Chemical structure of Sitagliptine IUPAC name: (3R)-3-amino-1-[3-(trifluoromethyl)-6,8-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one [37, 38]

Experimental part

A biguanide represented by Metformin and a sulfonylurea drug consisted of Glimepiride, have been tested. Their pharmacological action was compared with the one

Table 1
STATISTICAL INDICATORS OF HEMOGLOBIN (MEASURED IN g / dL) BY GENDER

Sex	Nr.	Average values	Standard deviation	Standard error	Confidence interval CI		Min.	Max.	ANOVA F Test (p value)
					- 95% CI	+95% CI			
Female	40	11.66	1.33	0.35	10.90	12.43	9.5	14.1	0.169
Male	40	12.30	1.14	0.28	11.69	12.91	10.1	14.0	
Total	80	12.00	1.25	0.23	11.54	12.47	9.5	14.1	

caused by alfa-glucosidase inhibitors, DPP- 4 inhibitors and insulin.

The study was performed on 80 patients diagnosed with type 2 diabetes mellitus which have been registered in the records of the diabetes and nutrition diseases section within Galati Hospital., aged between 38 and 87 years, sex ratio 1:1, (40 women and 40 men), with an average age of 64.30 ± 10.36 years in the female diabetic lot and 62.03 ± 11.87 years in the male lot, without statistically significant differences between 2 lots (p=0.364).

In the studied cases depending on the age distribution, it has been highlighted the following aspects:

- 22.5% of subjects are detected new cases;
- most cases have a length of up to 10 years (41.3%);
- 10% of subjects had an affection 21-30 years old.

All study group of patients underwent laboratory investigations: blood count, glycosylated haemoglobin, glycaemia level. It was monitored also the treatment with oral anti-diabetics and insulin in all three study stages: admission treatment, hospitalization and discharge treatment. Various therapeutic schemes used in the three stages were analyzed, but especially the medication changes throughout the study.

Statistic study

Some important statistic parameters were calculated in all the laboratory investigations: average values, standard deviation, standard error, confidence interval (± 95%), minimum, maximum values and ANOVA F-test through p value, to establish statistical differences between studied groups.

Results and discussions

Blood count analysis

Hemoglobin ranged from 9.5 to 14.1 g / dL, with a mean slightly lower in women (11.66 ± 1.33 g / dL) compared to that recorded in males (12.30 ± 1.14 g / dL), without showing significant statistical differences between two genders (p = 0.169) (table 1).

As shown in table 2, the number of white blood cells varried in the range 7.20 to 18 x 1000 / mL. There has been recorded an average value slightly higher in females (11.44 ± 1.47 x 1000 / mL) compared to that values recorded in males (11.09 ± 2.98 x 1000 / mL), without showing statistically significant differences between genders (p = 0.691).

At the studied cases, equality, there were no statistically significant differences in the average number of platelets (p = 0.318). The individual values ranged between 175 - 351 x 1000 / mL (table 3).

Glycosylated haemoglobin (HbA1c) analysis

Determination of glycated hemoglobin (HbA1c) was an assessment test and long term monitoring glycemic control for patients with diabetes. This test has been predictive for the risk of complications in diabetes: ketoacidosis, nephropathy, retinopathy.

It was the most effective therapeutic approach achieved by administering the oral anti-diabetes, and insulin. From the study performed no statistically significant differences were observed between the 2 female or male groups regarding glycated hemoglobin (p=0.972).

Determination of glycated hemoglobin (HbA1c) was an assessment test and long term monitoring glycemic control

Table 2
STATISTICAL INDICATORS OF WHITE BLOOD CELLS (n * 1000 / mL) BY GENDER

Sex	Nr.	Average values	Standard deviation	Standard error	Confidence interval CI		Min.	Max.	ANOVA F Test (p value)
					- 95% CI	+ 95% CI			
Female	40	11.44	1.47	0.39	10.60	12.29	9.50	14.10	0.691
Male	40	11.09	2.98	1.75	9.50	12.68	7.20	18.00	
Total	80	11.26	2.36	1.43	10.37	12.14	7.20	18.00	

Table 3
STATISTICAL INDICATORS OF PLATELETS (n x 1000 / mL) BY GENDER

Sex	Nr.	Average values	Standard deviation	Standard error	Confidence interval CI		Min.	Max.	ANOVA F Test (p value)
					- 95%CI	+ 95%CI			
Male	40	239.79	54.89	14.67	208.10	271.48	182	351	0.318
Female	40	213.65	80.14	20.69	169.27	258.03	175	338	
Total	80	226.27	69.18	12.85	199.95	252.58	175	351	

Gender	N	Average	Standard deviation	Standard error	Confidence interval		Min	Max	Test F (ANOVA) p
					- 95%CI	+95%CI			
Female	40	7.89	1.51	0.24	7.40	8.37	5.40	13.20	0.972
Male	40	7.90	1.61	0.25	7.38	8.41	5.50	12.00	
Total	80	7.89	1.55	0.17	7.55	8.24	5.40	13.20	

Table 4
STATISTICAL INDICATORS BELONGING HBA1C (%) SPLIT BY GENDER

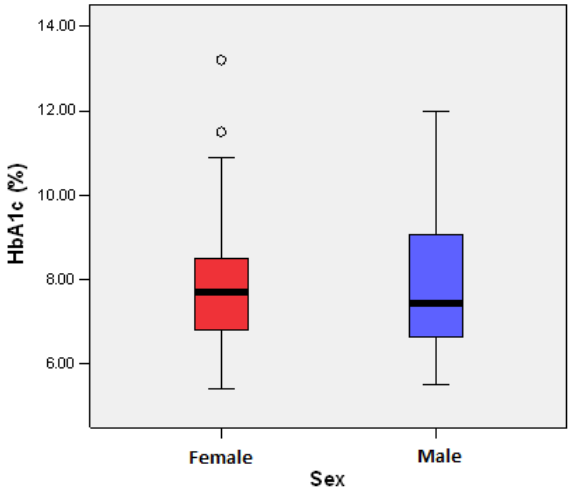

Fig. 7 The average values of HbA1c split by gender

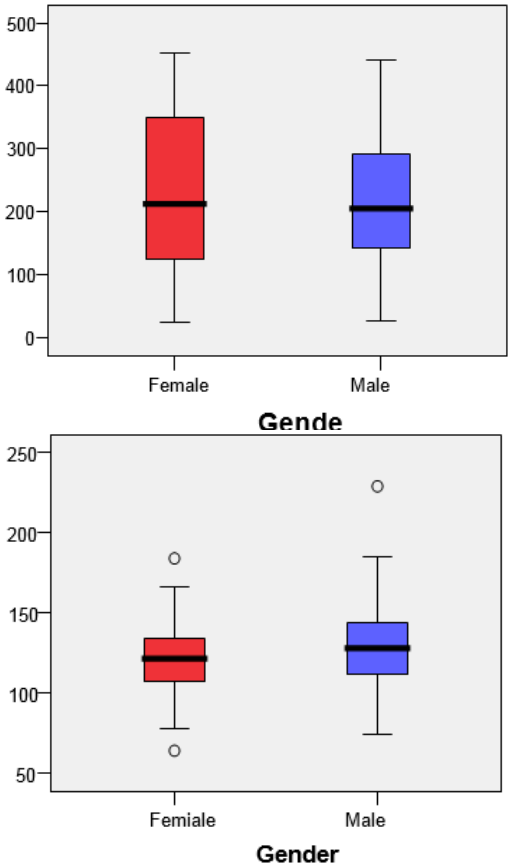

Fig.8. Mean blood glucose at admission and discharge by gender

for patients with diabetes. This test has been predictive for the risk of complications in diabetes: ketoacidosis, nephropathy, retinopathy.

It was the most effective therapeutic approach achieved by administering the oral anti-diabetes, and insulin. From the study performed no statistically significant differences

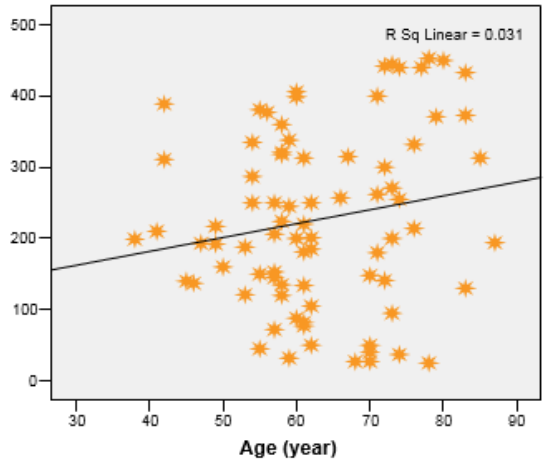

Fig 9 Correlation of blood glucose on admission depending on age

were observed between the 2 female or male groups regarding glycated hemoglobin (p=0.972).

Treatment prior admission

Depending on the epidemiological characteristics, the mono-therapy treatment (48.4% underwent mono-therapy) used prior admission highlighted the following aspects: sulfonylurea drugs were significantly more frequently used with the males (p=0.023) and patients suffering from diabetes for more than 10 years (p=0.001); biguanides were more frequently used with the males (p=0.003) and patients suffering from diabetes for less than 10 years (p=0.016); alpha-glucosidase inhibitors and DPP-4 (dipeptidyl peptidase) inhibitors did not show significant differences on genders, age groups or disease age (p>0.05); prior to admission insulin was more frequently used with the males (p=0.026). The analysis of the glycaemia values at admission on the basis of the therapeutic class used before admission reveals that in most cases of unbalanced diabetes mellitus, with glycaemia values between 150 and 250 mg/dL there are the patients treated with biguanides and sulphonylurea and in the least cases the patients treated with DPP-4 inhibitors, alpha glucosidase inhibitors and insulin (fig. 10).

Depending on the epidemiological characteristics, the treatment used during the admission showed the following

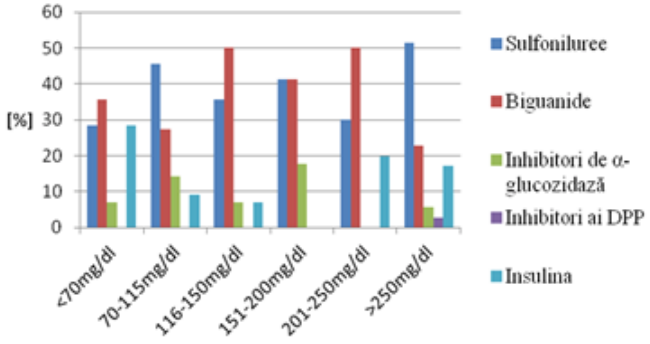

Fig. 10.Treatment prior based on glycaemia values at admission

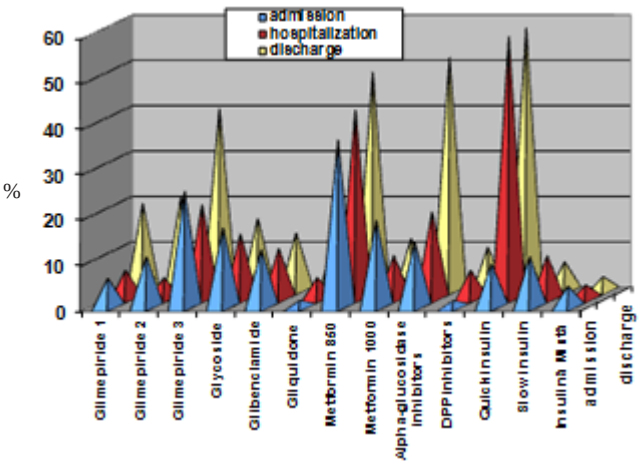

Fig.11. Distribution of diabetic patients depending on treatment

aspects: sulphonylureas were significantly more frequently used with females (p=0.025); biguanides were significantly more frequently used with females (p=0.040); alpha-glucosidase and DPP inhibitors did not show significant differences between genders, age groups or disease age (p>0.05**)** (fig. 10).

A percentage of 51.6% of the patients received combined therapy, the most frequent association in studied lot (20%) was between biguanides and sulfonylurea, followed with 16% by the combination between biguanides, sulfonylurea, á-glucosidase inhibitors. In equal shares (7%) are the combinations between biguanides, sulfonylurea and insulin, namely sulfonylurea and α-glucosidase inhibitors (fig.11).

Treatment during hospitalization

From 80 subjects, a percentage of 47.5% were treated during hospitalization with oral anti-diabetics, namely 47.5% with combined therapy (oral anti-diabetics and insulin) and only 5% were treated only with insulin (fig.11).

During the hospitalization, insulin was more frequently used with patients aged over 60 years (p=0.05). **T**he sulfonylurea treatment was administered to the patients with glycaemia over the reference value, yet significantly lower compared to the patients who did not receive this treatment type (p=0.004). Insulin was administered to patients with significantly high glycaemia level (p=0.001)(table 5).

Discharge treatment

The treatment recommended upon discharge shows the following differences depending on the epidemiological characteristics: sulphonylureaS were significantly more frequently recommended to patients aged more than 60 years (p=0.001); biguanides and DPP-4 inhibitors were recommended without significant differences between genders, age groups or disease age (p > 0.05); alfa glucosidase inhibitors were significantly more recommended to patients aged over 60 years (p=0.025); at discharge insulin was more frequently recommended to males (p=0.001), to patients aged over 60 years (p=0.001) and with diabetes age up to 10 years (p=0.049). The average glycaemia was slightly higher at patients who were recommended insulin (134.08 mg/dL). Class 1 obesity patients at discharge received treatment with sulphonylurea, biguanides and/or alpha-glucosidase inhibitors. The recommended treatment was not associated with the number of hospitalization days.

The treatment administered in one of the 3 study moments showed the following aspects: at prior admission, diabetic patients had most frequently Metformin and Glimepiride in their therapeutic scheme; during hospitalization Quick insulin and Metformin are most frequently administered; at discharge the therapeutic scheme is most frequently based on the administration of Quick insulin, alpha-glucosidase inhibitors, Metformin and Glimepiride.

Table 5

CORRELATION OF TREATMENT DURING HOSPITALIZATION WITH GLYCAEMIA ADMISSION

Treatment during hospitalization	N	Average	Std. deviation	Std. error	Confidence interval 95%		Min	Max	F Test (ANOVA) p value
					-95%CI	+95%CI			
Sulphonylurea									
No	47	259.64	129.22	18.85	221.70	297.58	27	453	**0.004**
Yes	33	180.27	99.96	17.40	144.83	215.72	25	406	
Biguanides									
No	48	245.85	139.30	20.11	205.41	286.30	25	453	**0.094**
Yes	32	198.47	90.66	16.03	165.78	231.16	37	406	
Alpha-glucosidase inhibitors									
No	68	227.53	129.41	15.69	196.21	258.85	25	453	0.915
Yes	12	223.33	89.32	25.78	166.58	280.09	72	406	
DPP-4 inhibitors									
No	76	228.01	126.65	14.53	199.07	256.95	25	453	0.728
Yes	4	205.75	40.73	20.36	140.94	270.56	153	250	
Insulin									
No	38	155.16	75.14	12.19	130.46	179.86	25	406	**0.001**
Yes	42	291.81	123.81	19.10	253.23	330.39	32	453	

Glicemie	N	Medie	Deviaţie Std.	Eroare Std.	Interval confidenţă 95%		Min	Max	Test F (ANOVA) p
					-95%CI	+95%CI			
La internare									
Feminin	40	237.35	133.41	21.09	194.69	280.01	25	453	0.454
Masculin	40	216.45	114.03	18.03	179.98	252.92	27	440	
Total	80	226.90	123.76	13.84	199.36	254.44	25	453	
La externare									
Feminin	40	120.70	24.28	3.84	112.93	128.47	64	184	0.207
Masculin	40	128.30	28.98	4.58	119.03	137.57	74	229	
Total	80	124.50	26.84	3.00	118.53	130.47	64	229	

Table 6
DESCRIPTIVE INDICATORS OF GLYCAEMIA BY SEX

Conclusions

The study established that biguanides + sulphonylurea do not provide an adequate glycaemic control, that insulin must be used on combination with metformin for the as quick as possible normalization of the glycaemia values, the glycaemia control is improved and the risk of hypoglycaemia is reduced at the obese patient on insulin therapy who is being administered biguanides. The periodic modification of the therapeutic schemes is necessary and it is explained by the fact that different anti-diabetics classes have different action mechanisms, which become ineffective when used for a long time, with the body's resources depletion. The most frequently used discharge treatment was represented by Metformin, Quick insulin, alpha-glucosidase inhibitors and Glimepiride in much larger doses than prior to admission. Along with the occurrence of diabetes complications increasingly larger doses of anti-diabetics are required.

Diabetes medication must be permanently adapted to the patient's needs, but also to the observance of their administration and association rules. The diabetic patient should use various therapeutic schemes, mainly based on the own insulin production and the sensitivity of each of them. The clinician should indicate as many medicine classes (plus insulin) as necessary so that the therapeutic objectives are reached. Prospective studies are required, which should monitor the diabetic patient's medication provided that the BMI is reduced and even normalized. It is necessary to discover and use new therapeutic classes for the adequate control of the glycaemia values.

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