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RESEARCH ARTICLE

DOSE TITRATION AND GLYCEMIC CONTROL WITH INSULIN GLARGINE 100 U/ML IN PREVIOUSLY UNCONTROLLED PATIENTS WITH TYPE 2 DIABETES: A 6-MONTH PROSPECTIVE OBSERVATIONAL STUDY IN PRIMARY CARE IN LEBANON.

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Abstract

Objective:the rapid increase in diabetes prevalence in lebanon is alarming, with 14.5% of the population affected in 2013. Early and adequate use of individualized insulin treatment strategies is effective to prevent or delay the onset of long-term complications. This study aimed at exploring the effectiveness of insulin glargine 100 u/ml (gla-100)-based strategies initiated at the discretion of primary care physicians (pcps) in people with type 2 diabetes mellitus uncontrolled on oral antidiabetic drugs (oads).

Research design and methods: in this national, multicenter, prospective study, 601 patients with previously uncontrolled type 2 diabetes and prescribed gla-100 were enrolled. Glycated hemoglobin (hba1c), fasting plasma glucose (fpg) and the changes in treatment schemes to reach control were analyzed after three and six months. Safety data were also reported.

Results:the majority (85%) of patients were overweight or obese, and over 30% had diabetes complications. About 60% of patients used a self-titration scheme and reported adherence to gla-100 therapy at both study visits. Hba1c decreased from 9.8 ± 1.3% (84 mmol/mol) to 7.1 ± 0.9% (54 mmol/mol) from baseline to 6 months ($p<0.0001$). Similarly, fpg levels significantly improved. People lost body weight of 1.7 kg at 6 months and only 1.4% reported minor hypoglycemic episodes.

Conclusion:this study demonstrated that introduction of gla-100 to type 2 diabetes patients uncontrolled on oad therapy significantly improved glycemic control with low risk of hypoglycemia and no weight gain. In addition, the study indicated that pcps in lebanon were successful in managing type 2 diabetes and monitoring patients' self-titration schemes.

Introduction:-

Population growth, aging, obesity and sedentary lifestyle all led to an increase in diabetes prevalence. The total number of diabetic patients worldwide was estimated since 2000 to increase from 171 million to 366 million in 2030 (1). This rapid increase in all countries is about 3% per year (2). Currently, the World Health Organisation (WHO)

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estimates 422 million cases worldwide and a rapidly rising prevalence, especially in middle- and low-income countries (3). This is particularly true in the Middle East and North Africa region where there were 34.6 million diabetic patients in 2014, and where the greatest increase in type 2 diabetes mellitus was observed in younger age groups (2). A recent study showed a large and increasing burden of diabetes in the Eastern Mediterranean Region (4). In particular, according to the International Diabetes Federation (IDF), about half a million cases of diabetes were counted in Lebanon in 2013, yielding a prevalence of about 14.5% among adults (2). Facing the rising global health threat, there is urgency in dealing with diabetes and its consequences. Recently, guidelines for the management of diabetes were published by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (5). Managing hyperglycemia is the main target of diabetes medical care as it is associated with adverse effects, hospitalization and increased mortality (6, 7). A systematic review and meta-analysis study showed that optimizing glycemic control can limit these complications in diabetic patients (8). The most used molecule to achieve glycemic control is insulin and attempts to prolong its action resulted in the clinical use of basal insulins (9, 10). For example, insulin glargine was developed to enhance insulin absorption by altering amino acid structure (9).

Controlled glycemia is defined as glycated hemoglobin (HbA1c) levels lower than 7% (53 mmol/mol) and fasting plasma glucose levels around 70 to 130 mg/dL as recommended by the ADA (11).

Despite these recommendations, a recent study, the International Diabetes Management Practices (IDMPS) study, conducted in Lebanon, showed that glycemic control was reached in 29.6% of type 2 diabetes patients with poorest outcomes seen for patients on insulin (12). Moreover, in Lebanon, data show that large numbers of patients rely on their primary care physicians (PCP) to manage their disease (13). For example, in the IDMPS study, the 17 PCPs who participated in the study reported consulting an average of 34 insulinized type 2 diabetes patients per month, compared to an average of 38 insulinized patients per month visiting specialists (12).

In the present study, type 2 diabetes patients were prescribed 3 insulin regimens over a period of 6 months and the objectives were to assess the change in HbA1c at 6 months compared to baseline and to evaluate effectiveness of the titration schemes in achieving glycemic targets, in addition to describing safety events reported during the study.

Research Design And Methods:-

Study design and patients.

In this national, multicenter, prospective study, patients were enrolled and followed up for 6 months. Investigators from all 6 Lebanese governorates were randomly selected from a list of primary care physicians (PCPs) routinely involved in diabetes management. The number of investigators in each governorate was proportional to the number of diabetic patients or to the number of identified PCPs, according to the availability of data in each governorate. To avoid bias, patients were included in the study sequentially. Eligible patients were adult (over 18 years of age) patients with previously uncontrolled type 2 diabetes, for whom the investigator had prescribed Gla-100 with or without an OAD or rapid insulin. Type 1 diabetes patients as well as patients with serious underlying illnesses, hospitalized or treated with Gla-100 within the previous year were excluded from the study. All enrolled patients who took at least one dose of Gla-100 were included in the safety population and those who met eligibility criteria and had at least two HbA1c values collected at baseline and one of the subsequent visits were included in the analysis population.

The study was approved by the Ethics Committee of the Hotel-Dieu de France Hospital in Lebanon. All participants provided written informed consent before enrolment into the study.

Data collection.

Data were collected for each patient on individual paper Case Report Forms (CRF) completed by the investigator or delegated staff at the baseline, 3-month and 6-month visits. The CRF collected patient demographics, vital signs, diabetes history and complications, associated comorbidities and related treatment, anti-diabetes treatment before study entry, HbA1c and FPG values, as well as prescribed insulin regimen and titration scheme. Adverse events (AEs) forms were used to collect non-serious AEs (NSAEs) and serious AEs (SAEs) and data displaying number of occurrences and number of patients reporting them was presented.

Definitions and study outcomes.
The primary objective of this study was to measure the change in HbA1c levels at 6 months compared to baseline. The secondary objectives were to evaluate the earlier changes in HbA1c levels, at 3 months, the percentage of patients achieving HbA1c < 7% (53 mmol/mol) at 3 and 6 months, the change in FPG values at 3 and 6 months and the change in treatment scheme to reach control. Safety data were also reported, in particular hypoglycemic events and weight changes.

Statistical methods.
In order to allow the estimation of changes in HbA1c levels at 6 months compared to baseline to within a maximum of 0.135% units using 95% confidence intervals (CI), 540 patients were needed. This sample size was also meant to allow for the detection of effect sizes as small as 0.14% in HbA1c change between baseline and 6 months using the paired t-test with 90% power and a significance level of 5%. It was then decided to recruit 600 patients into the study in order to account for about 10% loss to follow-up. Each investigator was expected to include 10 to 30 patients.

The analysis was performed on the overall analysis population. Numeric variables were summarized as follows: number of observed values, mean ± standard deviation (SD) with a two-sided 95% Wald CI, and value range for all endpoints. A paired t-test or a Wilcoxon signed rank test, depending on the normality of the data, was used to test the differences in HbA1c levels between baseline and 6 months. Categorical variables were described as follows: number of observed data, counts and percentages with a two-sided 95% CI using the Agresti-Coull method.

Results:-

Among the 601 patients enrolled over a period of 16.4 months and who signed the consent form, 9 were excluded for not having met the eligibility criteria and/or for having missing or invalid HbA1c values at both follow-up visits. Figure 1 gives patient disposition and overall participation in the study. Among all enrolled patients, 589 patients attended the 3-month visit and 592 patients attended the 6-month-visit, accounting for a total of 592 patients who were included in the analysis population. The mean age of these patients was 61.8±10.5 years, ranging from 27 to 94 years, and 57.8% of them were men. Table 1 gives patient demographics at baseline.

Medical history of study participants. The body mass index (BMI) was calculated for 553 patients as height measurements were missing for 39 patients. According to the WHO, weight is defined according to the following BMI categories: $18.5 \leq BMI < 25$ kg/m^2 is normal range, $BMI < 18.5$ kg/m^2 indicates underweight, $25 \leq BMI < 30$ kg/m^2 indicates overweight and $BMI \geq 30$ kg/m^2 indicates obesity. The BMI at baseline ranged from 15.2 to 60.5 kg/m^2 (mean = 29.8±4.9 kg/m^2). Less than 15% of patients had a BMI within the normal range, 0.5% were underweight and close to 85% were overweight (232 patients [42.0%]) or obese (239 patients [43.2%]).

Patients had diabetes for a mean duration of 8.9 ± 6.6 years, ranging from newly diagnosed to 43 years of living with the disease. Over 30% of patients suffered from at least one diabetes complication, notably coronary artery diseases (17.1%), cerebrovascular diseases (10.5%) and other diabetes complications (29.2%), such as peripheral vascular disease, diabetic neuropathy, nephropathy and retinopathy.

Prior to their enrollment in this study, 94.4% of the patients were treated with OADs only, 0.5% with injectable medications only and 5.1% with combination of both OAD and injectables. Frequency of OAD use was as follows: biguanides (95.4%), sulfonylureas (65.2%), dipeptidyl peptidase IV (DPP-IV) inhibitors (44.8%), thiazolidinediones (8.2%) or other OADs (1.5%). Injectables previously used included basal insulin (24.2%), rapid insulin (6.1%), premixed insulin (54.5%) and glucagon-like peptide 1 (GLP-1, 18.2%).

Almost 80% of patients reported at least one comorbidity (79.4%) and one concomitant treatment (78.2%). The most commonly reported comorbidities were vascular disorders (64.4%), metabolism and nutrition disorders (63.2%) and cardiac disorders (5.7%). In decreasing frequency, the most used concomitant medications were statins (50.2%), angiotensin II antagonists (35.0%), dihydropyridine derivatives (26.0%) and selective beta-blocking agents (23.8%). Prescriptions at baseline. All patients were prescribed Gla-100 at the baseline visit, given alone (basal) or with short-acting insulin (basal plus or basal bolus). As reviewed by Ampudia-Blasco *et al*, basal plus regimen is defined as one injection of rapid insulin at the main meal. Basal bolus regimen is defined as 2 or 3 injections of rapid insulin at different meals (14). At baseline visit, around 95% of patients were prescribed Gla-100 while only 1.5% and 3.5% of patients were prescribed basal plus and basal bolus regimens, respectively (Table 2). At the 3-month visit, 3.8%

of patients had their insulin regimen modified; decreasing to 2.6% at the 6-month visit. The distribution of patients in the different insulin regimen groups during the study visits and the modification of their insulin regimens are detailed in Table 2. All patients following the basal plus regimen took their rapid insulin shot at lunch. Among basal bolus regimen patients, 57.1% took their injections at two meals and 42.9% at all three meals.

The doses at which Gla-100 (basal regimen) and prandial insulin (basal plus and basal bolus regimens) were prescribed to patients at the three study visits are detailed in Table 3.

Titration scheme and adherence to therapy: At baseline, self-titration schemes were introduced to 386 of 592 patients (65.2%), of whom 78 (13.2%) had a titration scheme detailed according to their FPG levels (n=73 on Gla-100 alone, n=1 on basal plus, and n=4 on basal bolus). At month 3, self-titration schemes were prescribed to 343 of the 585 patients attending the visit. Of these 343 patients, only 31 (5.2%) had a titration scheme detailed according to their FPG level (n=25 on Gla-100 alone, n=1 on basal plus, and n=5 on basal bolus). Similar trends were observed at month 6, with 314 of 592 patients attending the visit still had prescribed a self-titration scheme. Only 29 (4.9%) patients had a scheme according to FPG levels (n=24 on Gla-100 alone, n=1 on basal plus, and n=4 on basal bolus). About 70% of patients on a basal plus or basal bolus regimen received rapid-acting insulin in addition to Gla-100 at baseline in a self-titration scheme. At 3 and 6 month visits, 82.4% and 61.9% of basal plus patients were still self-titrating. Conversely, the percentage of basal bolus patients self-titrating at month 3 (70.8%) went up to 83.3% at month 6. Most patients receiving basal or basal plus regimens followed a titration scheme every three days, while patients on basal bolus therapy mostly obeyed a daily titration scheme. From baseline to 6-month visit, target FPG slightly improved from 114.7±14.6 mg/dL to 110.6±11.6 mg/dL in patients on Gla-100 basal insulin regimen only, from 120.0±20.6 mg/dL to 115.0±10.0 mg/dL in patients on a Gla-100 basal bolus regimen and from 123.1±18.4 mg/dL to 120.7±16.4 mg/dL in patients on a Gla-100 basal plus regimen (Table 2). According to these targets, insulin dose increments changed from 2.9 U/day (baseline) to 2.3 U/day (6 months) for patients prescribed Gla-100. For patients following the basal plus regimen, insulin increments were about 2 U/days during all study visits, while for patients following the basal bolus regimen, Gla-100 dose was incremented by 2.3 U/day at baseline and by 2 U/day at the 3-month and 6-month visits (Table 3).

Adherence to the self-titration schemes was evaluated at the 3-month and 6-month visits. Out of the 585 patients who attended the 3-month visit and for whom self-titration data were available, 59.5% reported adherence to the titration scheme and 6.5% said they were not compliant. At the 6-month visit, 58.5% reported adherence to the titration scheme and 3.2% said they were not compliant. The most common reasons for non-adherence reported at both visits were the unpracticality of the titration scheme and the inherent poor overall adherence to treatments. None of the patients attributed non-adherence to occurrence of side effects.

Glycemic control with Gla-100 treatment: The effectiveness of the different insulin regimens was assessed according to HbA1c and FPG values (Table 2). Overall, 19% of patients achieved the HbA1c target of <7% (53 mmol/mol) after 3 months of treatment, increasing to 40% after 6 months. Mean HbA1c levels were significantly reduced from 9.8±1.3% (84 mmol/mol) with a 95% CI of 9.69-9.89% at baseline to 7.1±0.9% (54 mmol/mol, $p<0.001$), with a 95% CI of 7.07-7.21% at 6 months. Mean FPG levels were significantly reduced from 250.9±67.9 mg/dL (95% CI of 245.4-256.4 mg/dL) to 128.7±30.5 mg/dL (95% CI of 126.2-131.1 mg/dL) from baseline to 6 months ($p<0.001$).

Safety assessments. The safety analysis involved all 601 patients documented during follow-up. Body weight change and hypoglycemia events were specifically monitored. There was a downward trend in mean weight over the study period. At baseline, weight ranged from 49.0 to 180.0 kg (mean of 85.6±15.4 kg). Baseline weight had significantly decreased by 0.8±3.4 kg ($p<0.001$) at the 3-month visit and even further at the 6-month visit by a mean of 1.7±5.0 kg ($p<0.001$). Out of the 601 patients in the safety population, seven patients (1.2%) reported a total of eight hypoglycemia events: three asymptomatic episodes occurring in two patients (0.3%) and five symptomatic episodes in five patients (0.8%). None of the symptomatic episodes were reported as severe or serious.

In total, 96 adverse events (AEs) were reported by 88 patients (14.6%), of which 17 events in 15 patients (2.5%) were considered to be related to Gla-100. Only six AEs were reported as severe, 31 as moderate and 59 as mild. None resulted in treatment discontinuation. AEs included weight change (6.5% of patients), infections and infestations (4.8% of patients) and metabolism and nutrition disorders (1.3% of patients).

There were four serious AEs reported by four patients (0.7%) during this study, none of which was related to Gla-100. Two of these SAEs were moderate and two severe in intensity. Medication was discontinued in one case and two SAEs resulted in the death of two patients, both considered as not related to study drug.

Conclusions:-

Diabetes is a growing global burden, hence the rising need for optimizing its management. This is particularly true in middle- to low-income countries where unsatisfactory lifestyle habits are increasing the risk of diabetes. In Lebanon, the prevalence of diabetes in Greater Beirut was found to be close to 16% in 2005 (15) and complications of diabetes lead to relatively high occurrences of amputations especially in lower-income regions (16). Data also showed that in Lebanon, large numbers of patients rely on their PCP to manage their disease (11). Gla-100 has long been used to that end and to extend the availability of insulin for long periods. Historically, PCPs have preferred to treat patients with OAD agents rather than insulin (17). This may be due to many reasons mainly that patients and physicians are susceptible to fear and misconceptions about insulin therapy and disease progression (18). The primary aim of the present registry was to optimize at the primary care level the glycemic control and Gla-100 titration in newly diagnosed patients or whose diabetes was not controlled on other medications. This study followed the patients for a period of 6 months from the baseline visit where their Gla-100 scheme was designed, and then over two 3-monthly visits.

The large majority of patients were in the overweight and obese BMI categories. At study entry, over 94% of the patients were being treated with OADs. Almost 95% of them were prescribed basal Gla-100 with or without associated OAD, and the rest either basal plus (one rapid insulin injection at lunch time) or basal bolus.

Prescribed insulin regimens were re-evaluated at the 3-month visit. Overall, Gla-100 doses prescribed at baseline were increased at both the 3- and 6-month visits. Patients mostly complied with their titration scheme and non-adherence was mostly associated to the patients' personal poor adherence.

Though a rather modest decrease in HbA1c levels occurred after 3 months of treatment, mean levels of HbA1c decreased significantly by over 26% at the end of the study period (6 months). Similar trends were observed for FPG levels. Target HbA1c was achieved in about 40% of patients after 6 months at a mean Gla-100 dose of 26.5±9.5 units. Previous studies have already demonstrated the effectiveness of Gla-100 in controlling HbA1c levels in comparison to other forms of insulin (19, 20) and that patient-dependent adequate titration in the insulin dose can help patients reach their glycemic target (21).

Overall, the average weight of patients decreased over the study period, possibly contributing to better glycemic control (22) and only 1% of patients reported hypoglycemia events.

In summary, patients responded well to the prescribed insulin regimens. This study shows that PCPs were successful in managing diabetes and in monitoring patients' self-titration scheme, in accordance with previous studies reporting that PCP are just as proficient as specialists at titrating basal insulin therapies (23). However, current therapeutic approaches do not rely exclusively on basal insulin anymore since attempts were made to introduce novel long-acting insulin forms to the treatment of diabetes (24) and combinations of insulin to different anti-diabetes agents are approved by health authorities for the management of type 2 diabetes (25, 26). This study provides insights on how PCPs implement diabetes treatment recommendations and on how titration schemes were followed with basal insulin treatment in Lebanon in daily clinical practice. The results demonstrated that it seems advantageous to combine different forms of insulin with different terms of action for the individualized treatment of diabetes.

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List of participating investigators

All participating physicians who have enrolled at least one patient in the registry: Mohammad Hout, Grace Abi Rizk, Fadi Irani, Daniel Achkar, Mohammad Yassin, Varouj Bedirian, Michel Maalouly, Nada Atwi, Fadi Zaarour,

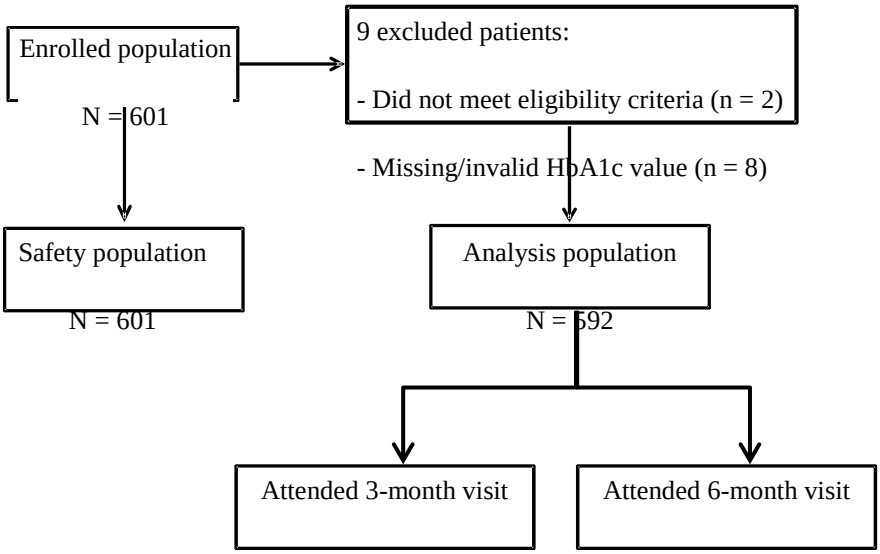

Figure 1:-Disposition of patients

Table 1:-Patient demographics at baseline

	Baseline N = 592
Male gender, n (%)	342 (57.8%)
Age in years, mean ± SD	61.8 ± 10.5
Distribution of patients in the age categories, n (%)	
[0-55[years	135 (22.8%)
[55-62[years	143 (24.2%)
[62-68[years	147 (24.8%)
Above 68 years	167 (28.2%)
Weight in kilograms	
Mean ± SD	85.4 ± 14.8
Median	85.0
Comorbidities, n (%)	
At least one comorbidity reported	470 (79.4%)
Hypertension	379 (64.0%)
Dyslipidemia	368 (62.2%)
Hyperuricemia	25 (4.2%)
Cardiovascular disorder	21 (3.6%)
Diabetes history	N = 573
Time since diagnosis in years	
Mean ± SD	8.9 ± 6.6
Median	7.0
Distribution of patients in categories of diabetes duration in years, n (%)	
[0-4[years	107 (18.7%)
[4-7[years	153 (26.7%)
[7-13[years	168 (29.3%)
Over 13 years	145 (25.3%)
Use of OADs, n (%)	
Biguanides	562 (94.9%)
Sulfonylureas	384 (64.9%)

DPP-4 inhibitors	264 (44.6%)
Thiazolidinediones	48 (8.1%)

DPP-4 inhibitors: dipeptidyl peptidase-4 inhibitors; SD: standard deviation; OAD: oral antidiabetic drugs.

Table 2:-Change in glycemia values and insulin regimen prescriptions during follow-up

		Baseline N = 592	3 months N = 585	6 months N = 591
Glycemia values				
*HbA1c in %**		N = 592	N = 336	N = 592
Range		7.5-15.0	5.7-10.5	5.4-10.5
Mean ± SD		9.8 ± 1.3	7.8 ± 0.9	7.1 ± 0.9
95% CI		9.69-9.89	7.69-7.89	7.07-7.21
FPG in mg/dL		N = 587	N = 345	N = 589
Range		77-493	70-323	70-312
Mean ± SD		250.9 ± 67.9	153.5 ± 39.3	128.7 ± 30.5
95% CI		245.4-256.4	149.4-157.7	126.2-131.1
Insulin regimen prescribed				
Basal (Gla-100)		562 (94.9%)	544 (93.0%)	544 (92.1%)
Basal plus		9 (1.5%)	17 (2.9%)	21 (3.6%)
Basal bolus		21 (3.6%)	24 (4.1%)	26 (4.4%)
Change in regimen, n (%)			22 (3.8%)	15 (2.6%)
Regimen at baseline	*Regimen at visit:*			
Basal	Basal plus		10 (45.5%)	5 (33.3%)
	Basal bolus		6 (27.3%)	5 (33.3%)
Basal plus	Basal		1 (4.6%)	2 (13.3%)
	Basal bolus		1 (4.6%)	0 (0.0%)
Basal bolus	Basal		4 (18.2%)	2 (13.3%)
	Basal plus		0 (0.0%)	1 (6.7%)
Change in Gla-100 self-titration scheme				
Basal (Gla-100)		N = 364	N = 318	N = 287
Target FPG (mean ± SD, mg/dL)		114.7 ± 14.6	112.2 ± 11.7	110.6 ± 11.6
Insulin increment (mean ± SD)		2.87 ± 2.94	2.28 ± 0.71	2.26 ± 0.68
Basal plus				
Self-titration of rapid insulin, n (%)		N = 9	N = 13	N = 13
Target FPG (mean ± SD, mg/dL)		120.0 ± 20.6	117.7 ± 13.6	115.0 ± 10.0
Insulin increment (mean ± SD)		2.00 ± 0.00	2.08 ± 0.28	2.08 ± 0.28
Basal bolus				
Self-titration of rapid insulin, n (%)		N = 13	N = 12	N = 14
Target FPG (mean ± SD, mg/dL)		123.1 ± 18.4	120.0 ± 16.5	120.7 ± 16.4
Insulin increment (mean ± SD)		2.31 ± 0.75	2.00 ± 0.00	2.00 ± 0.00

CI: confidence interval; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; OAD: oral antidiabetic drugs; SD: standard deviation.
*For clarity purposes, HbA1c values in the table were not converted to mmol/mol; HbA1c of 5.0% is equivalent to 31 mmol/mol.

Table 3:-Daily doses of basal and rapid insulin (in units) at the 3 visits and per meal

	Baseline visit	3-month visit	6-month visit
Basal (mean ± SD [min-max])	17.4 ± 8.1 [5-50]	23.8 ± 9.1 [5-60]	24.9 ± 10.0 [3-70]
Basal plus (mean ± SD [min-max])*	3.8 ± 1.5 [2-6]	5.9 ± 3.7 [2-14]	5.8 ± 3.3 [2-10]
Basal bolus (mean ± SD [min-			

max])	6.1 ± 2.2 [4-10]	7.4 ± 3.0 [4-12]	7.3 ± 4.2 [2-14]
At breakfast	6.1 ± 2.5 [2-10]	7.3 ± 3.0 [4-12]	7.3 ± 3.6 [2-14]
At lunch	5.3 ± 1.7 [2-10]	5.9 ± 1.9 [4-10]	5.9 ± 2.8 [2-10]
At dinner			

*All patients prescribed basal plus insulin regimen took their rapid insulin injection at lunchtime.
Max: maximum; Min: minimum; SD: standard deviation

References:-

1. Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes Estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-1053.
2. IDF Diabetes atlas,2013. Available from www.idf.org/diabetesatlas
3. World Health Organization Diabetes Fact Sheet. Available from http://www.who.int/mediacentre/factsheets/fs312/en/. Accessed 27 November 2016.
4. GBD 2015 Eastern Mediterranean Region Diabetes and CKD Collaborators, Mokdad AH. Diabetes mellitus and chronic kidney disease in the Eastern Mediterranean Region: findings from the Global Burden of Disease 2015 study. Int J Public Health 2017. doi: 10.1007/s00038-017-1014-1.
5. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; 35(6):1364-1379.
6. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemiarelated mortality in critically ill patients varies with admission diagnosis. Crit Care Med 2009;37:3001-3009.
7. Kotagal M, Symons RG, Hirsch IB, Umpierrez GE, Dellinger EP, Farrokhi ET, Flum DR; SCOAP-CERTAIN Collaborative. Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. Ann Surg 2015;261:97-103.
8. Murad MH, Coburn JA, Coto-Yglesias F, Dzyubak S, Hazem A, Lane MA, Prokop LJ, Montori VM. Glycemic control in non-critically ill hospitalized patients: a systematic review and meta-analysis. J Clin Endocrinol Metab 2012;97:49-58.
9. Bolli GB, Di Marchi RD, Park GD, Pramming S, Koivisto VA. Insulin analogues and their potential in the management of diabetes mellitus. Diabetologia 1999;42:1151-1167.
10. Chapman TM, Perry CM. Insulin detemir: a review of its use in the management of type 1 and 2 diabetes mellitus. Drugs 2004;64:2577-2595.
11. American Association of Diabetes. Available from http://www.ndei.org/ADA-diabetes-management-guidelines-diagnosis-A1C-testing.aspx.html
12. Azar ST, Malha LP, Zantout MS, Naja M, Younes F, Sawaya MT. Management and Control of Patients with Type 2 Diabetes Mellitus in Lebanon: Results from the International Diabetes Management Practices Study (IDMPS). J Med Lib 2013;61(3):127-131.
13. Adib SM, Nuwayhid I, Hamadeh GN. Most common diseases treated in primary health care facilities in Lebanon. J Med Liban 1995;43(1):17-22.
14. Ampudia-Blasco FJ, Rossetti P, and Ascaso JF. Diabetes Technol Ther2011;13(S1):S-75-S-83. https://doi.org/10.1089/dia.2011.0001
15. Hirbli KI, Jambeine MA, Slim HB, Barakat WM, Habis RJ, Francis ZM. Prevalence of diabetes in greater Beirut. Diabetes Care 2005;28(5):1262.
16. Yaghi K, Yaghi Y, McDonald AA, Yadegarfar G, Cecil E, Seidl J, Dubois E, Rawaf S, Majeed A. Diabetes or war? Incidence of and indications for limb amputation in Lebanon, 2007 East Mediterr Health J. 2012;18(12):1178-1186.
17. Hayes RP, Fitzgerald JT, Jacober SJ. Primary care physician beliefs about insulin initiation in patients with type 2 diabetes. Int J Clin Pract. 2008; 62:860-868.
18. Riddle MC. The underuse of insulin therapy in North America. Diabetes Metab Res Rev2002;18(S3):S42-S49.
19. Rosenstock J. Insulin therapy: Optimizing control in type 1 and type 2 diabetes. Clin Cornerstone 2001;4:50-64.
20. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: A meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. Diabetes Care 2005;28:950-955.
21. Barnett A. Dosing of Insulin Glargine in the Treatment of Type 2 Diabetes.Clin Ther 2007;29(6):987-999.

22. Rosenstock J, Shenouda SK, Bergenstal RM, Buse JB, Glass LC, Heilmann CR, Kwan AYM, Macconell LA, Hoogwerf BJ. Baseline Factors Associated With Glycemic Control and Weight Loss When Exenatide Twice Daily Is Added to Optimized Insulin Glargine in Patients With Type 2 Diabetes. Diabetes Care 2012;35(5):955-958.
23. Unger J. Insulin initiation and intensification in patients with T2DM for the primary care physician. Diabetes Metab Syndr Obes. 2011;4:253–261.
24. Rosenstock J, Bergenstal RM, Blevins TC, Morrow LA, Prince MJ, Qu Y, Sinha VP, Howey DC, Jacober SJ. Better glycemic control and weight loss with the novel long-acting basal insulin LY2605541 compared with insulin glargine in type 1 diabetes: a randomized, crossover study. Diabetes Care 2013;36(3):522-528.
25. Tzefos M, Olin JL. Glucagon-like peptide-1 analog and insulin combination therapy in the management of adults with type 2 diabetes mellitus. Ann Pharmacother 2010;44:1294-1300.
26. Thong KY, Jose B, Sukumar N, Cull ML, Mills AP, Sathyapalan T, Shafiq W, Rigby AS, Walton C, Ryder RE; ABCD Nationwide Exenatide Audit Contributors. Safety, efficacy and tolerability of exenatide in combination with insulin in the Association of British Clinical Diabetologists nationwide exenatide audit. Diabetes Obes Metab 2011;13:703-710.