

Insulin Versus Oral Hypoglycemic Drug Combination In Controlling Hyperglycemia In HCV Patients During Interferon Therapy

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Abstract: Hepatitis–C virus is common in many areas of the world particularly in Egypt and interferon therapy helps around 40 % of the patients to eradicate the virus and good glyceemic control is needed to get better results of interferon therapy This work aimed to study the efficacy of insulin therapy compared to oral hypoglycemic drugs in HCV patients receiving interferon therapy. Ninety six patients were included in the study divided into three groups (A) TREATED WITH INSULIN (B) treated with oral hypoglycemic drugs and (C) treated with two oral hypoglycemic drugs plus a bed time basal insulin. HbA1c,AST, ALT and the weight of the patients were measured at the start before intervention and 3 months after intervention.Results this study showed that insulin therapy – group-A - is more effective than oral hypoglycemic drug combination group-B and also more effective than group-C - treated with oral drugs and basal insulin – in reducing HbA1c ($p = 0.001$) and in improving weight and reducing AST AND ALT ($P < 0.05$). Also oral drugs plus a basal insulin at bed time - group – C was more effective than oral drug combination alone (group-B)in reducing HbA1c and the difference was statistically significant $p < 0.05$ and improving weight $p < 0.05$ and improving AST AND ALT but the results are statistically non significant ($p=0.09$ and 0.07). Conclusion insulin therapy is more effective than oral hypoglycemic drug combination in controlling blood glucose, improving liver enzymes and prevention of weight loss with some weight gain.

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1. Introduction:

Hepatitis –C virus (HCV) is causing a major problem in Egypt as it is widely spread and affects near 15 - 20 % of the general population (1)

A clear link is present between type -2 diabetes mellitus (T2 DM) and HCV infection, about 25 - 40% of HCV patients have T2 DM and One tenth of T2DM has HCV(2)

Control of diabetes in HCV patients is more difficult due to the state of sever insulin resistance, the presence of and Islet cell anti bodies and the presence of many inflammatory cytokines (3- 6)

Interferon (INF) is widely used for treatment of selected patients with HCV and up to 40 % of patients became HCV negative after 48 weeks of INF therapy (7)

Diabetic control is one of the parameters that affect the response of INF therapy in HCV patients (8- 11)

Many oral dugs and many types of insulin are used to control T2 dm HCV patients during INF therapy and most of the patients on oral drugs need combination therapy to achieve good glyceemic control (12)

The work aimed at comparing the efficacy and safety of oral hypoglycemic drug (s) and insulin in HCV patients treated with interferon.

2. Patients and Methods

Ninety six patients with uncontrolled (T2 DM) and HCV receiving a single weekly INF SC injection - there age ranged from 35 to 45 years old, 51 males and 43 females whom HbA1c ranged from 7.9 to 10.4 mg % before intervention treated with different oral drugs (mono-therapy or combination therapy. Careful medical history and clinical examination were done for all patients and patients with thyroid disorders or highly elevated liver enzymes were excluded HbA1C, AST & ALT and body weight were measured before intervention and three months later at the end of the study.

Patients are divided into three groups
Group –A Included 36 patients for whom premixed insulin was given before breakfast and dinner in suitable doses with adjusting the doses every 3 weeks according to the fasting and post meal glucose readings with a third pre lunch dose of regular insulin if needed

Group - B Included 36 patients for whom oral hypoglycemic drugs were given (metformin-SU- DDP-4 inhibitors- and TZDs) in different combination using the maximum dose of up to three drugs of the above mentioned groups.

Group -C Included 24 patients in whom the HbA1c was below 9 mg% and they were given the maximum dose of two oral drugs as mentioned in group -B plus adding a bed time basal insulin 10 to 20 unites.

All groups were given the medications regularly for 3 months and doses are adjusted every 3 weeks according to blood sugar readings

Statistical analysis

The data was analyzed with the program Statistical Package for Social Science (SPSS) under windows version 11.0.1. The following tests were used: Calculation of the mean value, Student t-test, Chi-square test (χ^2).

The probability of error (P) was expressed as following:

p - value > 0.05: non-significant (NS).

p - value \leq 0.05: significant (S).

p - value < 0.001: highly significant (HS).

3. Results

Ninety six patients with uncontrolled (T2 DM) and HCV receiving a single weekly INF SC injection - there age ranged from 35 to 45 years old, 51 males and 43 females whom HbA1c ranged from 7.9 to 10.3 mg % there age ranged from 35 to 45 years divided into three groups, group A included 36 patients and were given premixed insulin and group - B included 36 patients given up to the maximum dose of up to 3 drug from metformin, SU, DPP4I & TZDs and group -C included 24 patients given two oral drugs up to their maximum dose plus a bed time 10-20 unites of basal insulin. in all patients measurement of weight, Hb1ic, AST & ALT was done before intervention 3 months later and the results are:

All patients included in the study initially have uncontrolled diabetes and have nearly similar AST AND ALT & body weight

Table-1 Summary of patients data before and after treatment (Mean \pm SD)

	No	Before intervention					3 months after intervention				
		Weight (kg) Mean \pm SD	BMI Mean \pm SD	HbA1c (gm%) Mean \pm SD	AST (mg %) Mean \pm SD	ALT mg % Mean \pm SD	Weight (kg) Mean \pm SD	BMI Mean \pm SD	HbA1c (mg %) Mean \pm SD	AST (mg %) Mean \pm SD	ALT (mg%) Mean \pm SD
Group-A	36	61.5 \pm 2.4	22.3 \pm 1.5	8.95 \pm 0.8	34.2 \pm 2.1	50.1 \pm 2.3	62.8 \pm 2.8	22.9 \pm 1.7	7.50 \pm 0.8	32.27 \pm 2.3	45.09 \pm 2.5
Group-B	36	61.6 \pm 2.6	22.34 \pm 1.6	8.88 \pm 0.9	34.3 \pm 1.9	49.5 \pm 2.6	60.3 \pm 3.1	21.8 \pm 2.1	8.15 \pm 0.6	37.72 \pm 2.6	51.60 \pm 2.8
Group-C	24	61.8 \pm 3.1	22.4 \pm 1.3	8.13 \pm 1.1	35.7 \pm 2.1	49.8 \pm 3.1	62.1 \pm 2.4	22.6 \pm 1.9	7.57 \pm 0.9	37.27 \pm 2.9	50.1 \pm 3.2

Table -1 shows descriptive data of all the studied population in the three groups both at the start of the study - before intervention - and at the end of the study - 3 months after intervention.

Table -2 patient that achieved the target glycemic control (HbA1c less than 7 mg % in different groups

	Total number	NUMBER OF PATIENTS (HbA1c 7 mg% or less)	%
Group - A	36	22	6.1 %
Group - B	36	6	16.7 %
Group - C	24	9	37.5 %

This table showed that 61% of patients on insulin achieved glycemic control after 3 month while only 17 % of those on oral therapy achieved control and the difference between the two groups A and B is statistically highly significant ($p < 0.001$) and around 38 % of group -C patients achieved control and when comparing group -C to group - B the differences are statistically significant ($p= 0.03$) also the differences

between group -A and C are statistically significant ($p=0.04$)

Table -3 Comparison between different groups regarding to HbA1c values

Group	HbA1c before intervention	HbA1c 3-months after intervention	P - value
Group-A	8.95	7.50	0.003
Group-B	8.88	8.15	0.04
Group-C	8.13	7.57	0.03
		A compared to B	0.02
		A compared to C	0.8
		C compared to B	0.02

This table showed that patients on insulin therapy - group A - and patients on oral drugs plus bed time insulin - group C- achieved better HbA1c compared to those on oral drugs only - group B- and the differences are statistically significant ($p=0.02$). And patients on insulin therapy - group A - achieved

nearly the same HbA1c compared to patients on oral drugs plus bed time insulin – group C and the differences are statistically not significant ($p=0.8$)

Table -4 comparisons between different groups regarding body weight

Group	Weight before intervention	Weight 3- months after intervention	P - value
Group-A	61.5	62.8	0.3
Group-B	61.6	60.3	0.3
Group-C	61.8	62.1	0.3
		A compared to B	0.06
		A compared to C	0.4
		C compared to B	0.06

This table showed that patients on insulin therapy - group A - and patients on oral drugs plus bed time insulin – group C- achieved better weight gain compared to those on oral drug s only - group B- and the differences are statistically not significant ($p=0.06$). And patients on insulin therapy - group A - achieved better weight gain compared to patients on oral drugs plus bed time insulin – group C - and the differences are statistically not significant ($p=0.4$)

Table -5 comparisons between different groups regarding AST values

group	AST before intervention	ALT 3- months after intervention	P - value
Group-A	34.2	32.27	0.009
Group-B	34.3	37.72	0.005
Group-C	35.7	37.27	0.05
		A compared to B	0.001
		A compared to C	0.001
		C compared to B	0.5

This table showed that patients on insulin therapy - group A - achieved greater AST reduction compared to the other groups (those on oral drug s only - group B- and those on oral therapy and basal insulin the differences are statistically highly significant ($p=0.0001$). And patients on oral drugs plus basal insulin - group C - achieved nearly the same AST level compared to patients on oral drugs only– group B – (AST increased in both groups) and the differences are statistically not significant ($p=0.5$)

This table showed that patients on insulin therapy - group A - achieved greater ALT reduction compared to the other groups (those on oral drug s only - group B- and those on oral therapy and basal insulin the differences are statistically significant ($p=0.002$ and 0.003 respectively). And patients on oral

drugs plus basal insulin - group C - achieved nearly the same ALT level compared to patients on oral drugs only– group B – (ALT increased in both groups) and the differences are statistically not significant ($p=0.2$) m69-262-764

Table- 6 comparison between different groups regarding ALT values

group	ALT before intervention	ALT 3- months after intervention	p - value
Group-A	50.1	45.09	0.005
Group-B	49.5	51.60	0.3
Group-C	49.8	50.1	0.5
		A compared to B	0.002
		A compared to C	0.003
		C compared to B	0.2

Table -7: Comparing all groups as regard the hypoglycemic events

	Total number	Number of hypoglycemic events	Total
Group -A	36	2 sever and 5 mild	7
Group -B	36	3 sever and 7 mild	10
Group -C	24	0 sever and 6 mild	6

From this table it is clear that 2 sever plus 5 mild hypoglycemic attacks were reported in patients on insulin therapy - group –A-, while 3 sever and 7 mild attacks were reported in patients on oral therapy - group- B- especially when triple therapy is used but in group – C whom were given one or two oral drugs and a bedtime basal insulin no sever hypoglycemic events were detected while six mild hypoglycemic events were reported and the differences between the groups are statistically non significant

4. Discussion

This study included 96 HCV patients receiving INF in whom diabetes is badly controlled on a single oral hypoglycemic agent or two drug combination in the maximum allowed doses including 51 males and 42 females and their age ranged from 35 to 45 years old and their HbA1c ranged from 7.9 - 10.3 mg % and their AST AND ALT values were normal or slightly elevated, their weight and height are measured and the BMI was calculated and ranged from 19.1 to 22.8 as INF and hyperglycemia affected their weight Trying to control their hyperglycemia by either stopping the oral drugs and shifting to premixed insulin in two doses before breakfast and dinner (group – A) or adding a third drug (group-B) or adding a bed time basal insulin (group-C)

All patients are regularly followed up and their doses were re- adjusted every 3 weeks according to

their blood sugar readings and at the end of the study - after 3 months- HbA1c, AST, ALT and body weight were re-measured and data were analyzed and we found that 61% of patients on insulin achieved glycemic control after 3 months while only 17 % of those on oral therapy achieved control and the difference between the two groups A and B is statistically highly significant ($p < 0.001$) and around 38 % of group -C patients achieved control and when comparing group -C to group - B the differences are statistically significant ($p= 0.03$) also the differences between group -A and C are statistically significant ($p=0.04$)

Patients on insulin therapy - group A - and patients on oral drugs plus bed time insulin - group C- achieved better HbA1c compared to those on oral drugs only - group B- and the differences are statistically significant ($p=0.02$). And patients on insulin therapy - group A - achieved nearly the same HbA1c compared to patients on oral drugs plus bed time insulin - group C - and the differences are statistically not significant ($p=0.8$)

Patients on insulin therapy - group A - and patients on oral drugs plus bed time insulin - group C- achieved better weight gain compared to those on oral drugs only - group B- and the differences are statistically not significant ($p=0.06$). And patients on insulin therapy - group A - achieved better weight gain compared to patients on oral drugs plus bed time insulin - group C - and the differences are statistically not significant ($p=0.4$)

Patients on insulin therapy - group A - achieved greater ALT reduction compared to the other groups (those on oral drugs only - group B- and those on oral therapy and basal insulin the differences are statistically significant ($p=0.002$ and 0.003 respectively). And patients on oral drugs plus basal insulin - group C - achieved nearly the same ALT level compared to patients on oral drugs only- group B - (ALT increased in both groups) and the differences are statistically not significant ($p=0.2$)

Patients on insulin therapy - group A - achieved greater AST reduction compared to the other groups (those on oral drugs only - group B- and those on oral therapy and basal insulin the differences are statistically highly significant ($p=0.0001$). And patients on oral drugs plus basal insulin - group C - achieved nearly the same AST level compared to patients on oral drugs only- group B - (AST increased in both groups) and the differences are statistically not significant ($p=0.5$)

Two severe & 5 mild hypoglycemic attacks were reported in patients on insulin therapy (group -A), while 3 severe and 7 mild attacks were reported in patients on oral therapy - (group- B) especially when triple therapy is used but in (group - C) whom were

given one or two oral drugs and a bedtime basal insulin no severe hypoglycemic events were detected while six mild hypoglycemic events were reported and the differences between the groups are statistically non significant

Our results are consistent with Higgins et al. who reported that insulin is preferred to oral hypoglycemic drugs in hepatic patients (13)

United Kingdom Prospective Diabetes Study (UKPDS) in 1998 also stated that insulin gives better and greater HbA1c reduction if the initial HbA1c is higher (14). Also Narhan who stated that insulin gives better results in type -2 diabetic patients that oral drug combination (15)

Roaid et al. stated that oral hypoglycemic drugs are effective in treating diabetes in HCV patients but insulin is preferred during anti viral treatment (12)

An ongoing research in the National Taiwan university with early results published in the university web in 2009 stating that oral drug may not be effective in treating diabetic patients receiving interferon therapy (16)

The ADA report (2011) stated that all oral drugs are contraindicated if liver enzymes are highly elevated

Defranzo et al., (18) and Sherifali et al.,(19) studied the HbA1c lowering effect of the currently used anti diabetic agents and found that insulin had the highest power followed by combining insulin and oral and lastly oral agents alone

Harrison concluded that pioglitazone may improve glycemic control in insulin-resistant HCV patients (20).

Conclusion

Insulin therapy is more effective in controlling hyperglycemia in T2DM and HCV during interferon therapy with also improvement of liver enzymes and stoppage of weight loss noticed in those patients compared to oral hypoglycemic drugs even if insulin is given once daily with oral drugs patients will get better glycemic control.

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