Efficacy of Adding Metformin to Pegylated Interferon and Ribavirin in Treatment Naïve Patients with Chronic Hepatitis C: A Randomized Double-Blind Controlled Trial

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ABSTRACT

BACKGROUND

Evidence indicates that insulin resistance results in poor sustained viral response (SVR) in patients with chronic hepatitis C (CHC). Metformin is an oral hypoglycemic agent which improves insulin resistance.

METHODS

We sought to determine if the addition of metformin to the treatment regimen could improve SVR in treatment-naïve CHC patients in a randomized, double-blind, placebo-controlled trial. We randomized 140 consecutive CHC patients to receive either metformin 500 mg three times a day or placebo in addition to pegylated interferon (PEG-IFN) and ribavirin (RBV). Only treatment-naïve subjects aged between 15 and 65 years of age were included. SVR was defined as no detectable HCV RNA six months after the end of treatment. Subjects who received at least one dose of PEG-IFN were included in the final analysis.

RESULTS

The SVR rate in the metformin group was 75% versus 79% in controls (intention-to-treat) which was not significantly different. Also, the difference between the placebo and metformin group was not significant in subsets of different genotypes or those with homeostasis model assessment of insulin resistance (HOMA-IR) levels greater than 2 or body mass index greater than 25. The most common complaint was gastrointestinal discomfort (13% in metformin group versus 4% in controls; p=0.002) that lead to discontinuation of metformin in 8 participants.

CONCLUSION

Although triple therapy with metformin, PEG-IFN and RBV is relatively well tolerated, the addition of metformin did not significantly improve viral response in CHC patients.

KEYWORDS
Metformin; Hepatitis C; Insulin resistance

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INTRODUCTION

Insulin resistance and diabetes are major disease modifiers in chronic hepatitis C (CHC).[1] There is evidence for a role of insulin resistance, the

best predictor of type 2 diabetes mellitus, in failure to achieve sustained viral response (SVR) in patients with CHC.[1-3] Also, insulin resistance has been associated with fibrosis progression, development of steatosis and greater risk of developing hepatocellular carcinoma in those infected with CHC.[4,5] In several prospective studies of CHC patients, higher fasting insulin levels and higher homeostasis model assessment of insulin resistance levels (HOMA-IR) were all independently associated with a poor viral response to therapy even in patients traditionally considered as those who responded very well to treatment.[3] Likewise it has been shown that patients who have previously failed anti-viral therapy have greater insulin resistance.[2]

Metformin is known to induce AMP-activated protein kinase (AMPK) through inhibition of AMP deaminase. AMPK is involved in both lipid and glucose metabolism. It also effectively inhibits viral replication.[6] It appears that infection of the hepatocyte with hepatitis C virus (HCV) leads to phosphorylation of AMPK resulting in reduced activity and thus enhanced viral replication as well as lipid accumulation.[7] Subsequently, it has been suggested that restoration of AMPK activity can inhibit viral replication. Metformin is known to induce AMPK through inhibition of AMP deaminase and this is the probable mechanism by which metformin, as well as other insulin sensitizing agents, may improve SVR in subjects with CHC.[8,9] There are a few studies which have investigated this idea but the results are far from convincing.[10-14]

There might also be other benefits for using insulin sensitizers in CHC such as a reduction in hepatocellular carcinoma or metabolic benefits from improvement in insulin resistance.[5,12,15,16]

The present study is a double-blind randomized controlled trial designed to investigate the efficacy and safety of adding metformin to pegylated interferon (PEG-IFN) and ribavirin (RBV) in non-diabetic treatment-naïve patients with CHC.

MATERIALS AND METHODS

Subjects

The study was performed in the Shariati Hospital HCV clinic which is a tertiary referral center affiliated with Tehran University of Medical Sciences. We enrolled 140 consecutive treatment-naïve patients with CHC who were considered eligible for treatment.

Table 1: Exclusion criteria.

Pregnant or willing to become pregnant in the next 18 months.
Unable to use effective contraception during the next 18 months.
Diabetes mellitus
Contraindication for treatment with pegylated interferon (PEG-IFN), ribavirin (RBV) or metformin.
Significant liver dysfunction (albumin <3 gr/dl, prothrombin time >15sec)
Decompensated cirrhosis (Child-Pugh scores B or C)
Concurrent hepatitis B or human immunodeficiency virus infection
Autoimmune hepatitis
Primary biliary cirrhosis
Sclerosing cholangitis
Renal failure (creatinine >1.5 mg/dl for males and >1.4 mg/dl for females)
Severe medical conditions (e.g., heart failure, hypoxic acidosis, psychosis, etc.)
Refusal to provide consent for study participation.

Entry criteria included male and female patients aged between 15 and 65 years who were HCV RNA positive and had evidence of HCV infection for at least 6 months. Exclusion criteria are summarized in Table 1.

Clinical and laboratory assessments

We collected data on age, sex, weight, height, waist and hip circumference. The body mass index (BMI) was calculated as weight (kg) divided by the square of the height (meters).

After an overnight fasting of 12 hours, venous blood was drawn to determine hemoglobin, white blood cell count, platelet count, plasma glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), albumin, bilirubin, cholesterol (high- and low-density), insulin and C peptide.

A quantitative HCV-RNA polymerase chain reaction assay was used to determine baseline serum HCV-RNA levels (COBAS Amplicor HCV Monitor Test v 2.0, Roche Diagnostics, Mannheim, Germany). HCV genotypes were determined by melting curve analysis (MCA) using a single hy-

bridization probe.

HOMA-IR was calculated by the following equation: HOMA-IR = fasting plasma glucose (gr/dl) × fasting insulin level (mU/L)/405.

After obtaining verbal and written consents, all participants underwent percutaneous liver biopsies. The biopsies were scored according to Ishak et al.[17] Steatosis was assessed as the percentage of hepatocytes that contained macrovesicular fat droplets and graded as no steatosis (<5%), mild (<33%), moderate (33%-66%) or severe (>66%).

Treatment arms

All subjects received treatment at the time of enrollment in the study. Treatment included weekly injections of PEG-IFN (either 180 µg PEG-IFN alfa-2a or 1.5 µg/kg PEG-IFN alfa-2b) plus RBV 800, 1000, or 1200 mg per day depending on patient's weight and HCV genotype. Participants infected with genotypes 1 and 4 were treated for 48 weeks and those with genotypes 2 and 3 for 24 weeks. Furthermore, patients were randomized using a computer generated list to receive either 500 mg metformin three times daily or placebo for the treatment period (24 or 48 weeks depending on genotype). Both patients and researchers were blinded to the study medications.

Endpoints

The primary endpoint of the study was no detectable HCV RNA in serum six months after the end of treatment (SVR, Cobas Amplicor TM HCV Monitor v 2.0, Roche Diagnostics, Mannheim, Germany).

Ethics

The study protocol was approved by the Institutional Review Board and Ethics Committee of the Digestive Disease Research Institute of Tehran University of Medical Sciences and was registered in clinical trials.gov (ID: NCT00560690).

RESULTS

There were 140 participants enrolled in the study (70 participants per group). Of these, 135 subjects received at least one dose of PEG-IFN and were included in the analysis. The baseline characteristics of subjects are given in Table 2.

Table 2: Baseline characteristics of subjects.

Variables		Metformin	Placebo	Total
Sex (M/F)		60/8	57/10	117/18
Age (mean±SD, yrs)		41.5±11.2	41.9±11.0	41.7±11.1
Genotype	1 and 4	33	34	67
	2 and 3	35	33	
HOMA-IR (mean±SD)		1.88±1.50	2.14±1.81	2.00±1.66
BMI (mean±SD, kg/m/m)		24.2±3.9	24.8±3.1	24.5±3.6
Viral load (IU/ml)		4,186,000	2,732,000	3,459,000
Histologic grade (mean±SD)		6.2±2.8	5.8±2.5	6.0±2.7
Histologic stage (mean±SD)		1.8±1.6	1.5±1.3	1.6±1.4

There were 16 participants lost to follow-up (8 from each group). The SVR rate in the metformin group was 75% versus 79% in controls (intention-to-treat) which was not significantly different. The difference between the SVR of the two groups was not significant in the per-protocol analysis in subjects who completed the full course of treatment with PEG-IFN, RBV and metformin (or placebo). A subset of participants with insulin resistance (HOMA-IR >2) and a subset with BMI >25kg/m^2 were also analyzed. There was no significant difference in SVR between the placebo (p=0.20) and metformin (p=0.19) groups. The SVR for genotypes 1 and 4 subjects was 71.6% and for genotypes 2 and 3, 82.4%. The difference between the placebo and metformin groups was again non-significant when separately calculated for each genotype (p=0.26 for genotypes 1 and 4 and p=0.86 for genotypes 2 and 3).

The most common adverse event observed during treatment was gastrointestinal discomfort seen in 13% of metformin group patients and 4% of controls (p=0.002).These adverse events lead to discontinuation of metformin in 8 subjects.

DISCUSSION

It is well established that infection with HCV can induce insulin resistance and fat accumulation in the liver and multiple molecular mechanisms have

been described for this phenomenon.[18,19] There is further evidence that this insulin resistance provides some sort of survival advantage for the virus.[1,3,7,20,21] Such studies form the rationale for trials of insulin sensitizers in CHC with the assumption that reversing insulin resistance may deprive the virus of this advantage and hinder its replication.[12,22]

A few researchers have investigated metformin in CHC. Romero-Gomez et al. in a design very similar to ours randomized 123 consecutive patients with CHC genotype 1 to receive metformin versus placebo in addition to PEG-IFN and RBV. They failed to observe a significant benefit for metformin although a slight benefit was observed for female subjects.[14] The number of females with genotype 1 infection was too small in our study to allow any meaningful conclusion.

In a more recent study by Yu et al. 98 patients with genotype 1 were studied in a similar design and a significant advantage was observed for the metformin group although the p-value was borderline at 0.043.[11] In our study we did not observe a significant difference in genotype 1 subjects.

We also analyzed a subgroup of our patients with initially high HOMA-IR to see if metformin was more effective in this group but again failed to demonstrate any advantage. Neither did we find a benefit among overweight and obese subjects (BMI>25).

There are other proposed mechanisms for insulin resistance in CHC, one of which is through decreased activity of peroxisome proliferator activated receptor gamma(PPARγ).[23] Pioglitazone, a PPARγ agonist, has been studied in subjects with CHC with varying degrees of success but overall the results have been disappointing.[24-26]

By reviewing the literature it appears that any improvements in SVR by insulin sensitizers such as metformin are likely to be small.

We did not observe any benefit in adding metformin to the treatment of CHC in terms of improving SVR. Further research with larger number of patients will clarify this issue. However due to the recent approval of direct acting antivirals with very high SVR rates we doubt that such studies are justified.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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