DISCUSSION

For many years, Egypt has been widely regarded as having an epidemic, with the highest recorded HCV prevalence in the world. The latest published Egyptian Demographic Health Survey (EDHS) in 2009 was a national probability sample of the resident Egyptian population. This report estimated an overall anti-HCV antibody prevalence of 14.7%. The number of Egyptians estimated to be chronically infected was 9.8%. HCV is currently the most significant health problem in Egypt.[39, 58]

The current standard treatment of chronic hepatitis C (CHC) is pegylated interferon-α (peg IFNα) combined with ribavirin. Despite significant improvement in treatment efficacy during the past decade, only 50% of patients can be cured of HCV depending on its genotype. Besides being unsatisfactory, treatment of HCV is costly, beyond the reach of most patients, requires 48 or more weeks to complete and has serious side effects.[27] New modalities of therapy are available but not yet implemented in the national treatment program.

There is strong epidemiological evidence linking HCV and diabetes. Patients with CHC are more likely to develop T2D and diabetic patients are more likely to be infected with HCV. Type 2 diabetes has been recognized to worsen the course of hepatitis C. Both are now recognized as being a deadly combination. The association between HCV infection and glucose abnormalities is true if, instead of looking at the occurrence of overt T2D, prediabetic conditions, such as insulin resistance (IR) should be considered. [124, 125]

During the past years, basic research, clinical trials and epidemiological studies have provided evidence that HCV can independently contribute to IR. Adding to this growing body of evidence, it is now suggested that HCV interferes with insulin signaling pathway using genotype-specific mechanisms. Insulin carries its biological effects through phosphorylation of the substrate of the insulin receptor 1 (IRS-1) and 2 (IRS-2). [129] Thus research has focused on IRS-1 and IRS-2 as a locus for insulin resistance. The association between HCV and IR has significant clinical consequences. Mounting evidence indicates that HCV-associated insulin resistance may cause accelerated fibrogenesis, reduced response to IFN-based therapy and hepatocellular carcinoma. [139] Increased levels of IR are associated with reduced rates of initial virological response as well as sustained virological response in CHC patients treated with a combination of pegylated IFN-α and ribavirin. Conversely, development of insulin resistance or exacerbation of previously stable glycemic control has been reported as drug side effects in CHC patients who are receiving IFN treatment. Our aim was to study the inter-relationship between insulin resistance, metabolic factors and impact on treatment outcome with peg-interferon alpha and ribavirin, focusing on chronic HCV patients with genotype 4.[117, 129, 134]

This study assessed one hundred non-diabetic, histologically proven chronic hepatitis C patients (CHC) with genotype 4 infection attending the 'Centre for Treatment of Hepatitis Virus' in Sharq El Madina Hospital for insulin resistance by HOMA-IR over a period of 6 months for the prevalence study. Based on the results of the prevalence study, 71 consecutive non-diabetic treatment-naïve CHC patients were enrolled in the study for testing treatment outcome associated with various degrees of insulin resistance. Both groups were given a combination of pegylated interferon and ribavirin for an intended duration of 48 weeks. After 12 weeks, the early virological response was assessed by measuring the viral load and HOMA score was measured. Viral load and insulin resistance were re-assessed after 48 weeks of therapy. Liver biopsies were taken from the 100 CHC studied cases to assess degree of fibrosis, necroinflammation and steatosis, and to examine the level of IRS-1 protein expression by an immunohistochemical study (in selected cases). Body mass index was calculated, lipid profile was measured and metabolic syndrome assessed.

Among the 100 chronic HCV patients included in the study, 40 were males and 60 were females. The median age of the studied group was 45 years with a range of 19-59. Thirty one patients had HOMA-IR scores >3.0 indicating insulin resistance. The distribution of the 100 chronic HCV patients included in the study with respect to their viral load was as follows: 22% had low level viremia, 43% had intermediate level viremia and 35% had high level viremia. The median of the BMI of the 100 CHC patients included in the study was 27.60 with mean ± SD 27.06 ± 3.44. Metabolic syndrome was present in 15% of them. According to the Metavir system, liver biopsies of the 100 CHC patients included in the study showed that necroinflammatory activity in liver biopsies of these patients was as follows: 55% A1, 44% A2, 1% A3 and none was graded as A0. Fibrosis staging was 51% F1, 45% F2, 4% F3 and none were F0 or F4. Steatosis was not found in 48% of cases, mild in 20.7%, moderate in 20.7% and severe in 10.3%. As for the immunohistochemical studies for IRS-1 of 29 selected liver sections of these patients, 15 cases showed weak staining of 10-50% or less of hepatocytes and 14 cases showed strong staining of 50% or more of hepatocytes.

The correlational studies between insulin resistance and age, BMI, basal viral load, lipid profile, fibrosis staging and steatosis grading, showed statistically significant difference between HOMA-IR and basal viral load and fibrosis stage. When the data were analyzed by multivariate linear regression, results suggested that basal viral load remained the only independent factor associated with elevated HOMA-IR levels ($p=0.001$). The follow up studies of HOMA-IR of the cEVRs in 54 patients showed that there is statistically significant difference ($p<0.001$) between the pretreatment HOMA-IR, after 12 weeks of therapy and at the end of treatment, denoting significant decline in the HOMA score values at the three different measurements. As for the relation between insulin resistance and treatment response, there was statistically significant difference ($p=0.006$) between the HOMA-IR of the early non-responders, pEVR and cEVR group of patients. As for the univariate analysis of pretreatment variables affecting treatment outcome, this study revealed that the younger age, lower HOMA-IR scores, lower baseline HCV

RNA level and lower grades of steatosis, were significantly associated with end of treatment response of our studied CHC patients. The multivariate logistic analysis showed that the lower baseline viral load remained the only independent factor associated with end of treatment response.

The current study comprised 100 patients with chronic HCV infection, 40 were males and 60 were females. The median age of the studied group was 45 years with a range of 19-59. Chehadah *et al* studied non-diabetic CHC patients; 70% were males and 30% were females with median age of 44 years and a range of 21-71.[164] Brandman *et al* studied CHC patients, 57% were males with median age of 48 years.[137] Khattab *et al*'s study included 52% males with median age of 40 years.[142] Moucari *et al* studied a group of CHC patients, 74% were males with median age of 45 years.[144] Ziada *et al* studied CHC patients whose median age was 42 years.[131] Similarly, De souza *et al*'s study was on patients whose median age was 51 years, where 51% were males and 49% were females.[139] Thus the median age of the group of patients studied in this series is closely similar to the previously mentioned studies. As for the gender of the studied group, variation may be due to the randomization in the selection of the group of patients studied.

Chronic hepatitis C has many features which suggest that this disease must be viewed not only as a viral disease but also as a metabolic liver disease which implies: insulin resistance, increased prevalence of impaired glucose tolerance and changes in lipid metabolism. These findings suggest that chronic HCV infection is closely related to the metabolic syndrome, both are common conditions worldwide.[165] In this series, we found that metabolic syndrome, according to the recently revised WHO definition [147], was present in 15% of patients having CHC. The mean ± SD BMI of the same cohort of patients was 27.06 ± 3.44 kg/m^2. Similarly, Khattab *et al* genotype 4 CHC group of patients had baseline pretreatment BMI mean ± SD of 24.64 ± 3.34 kg/m^2.[142] Brandman *et al* also had similar results where the patients included in their study had BMI mean ± SD of 26 ± 4 kg/m^2.[137] Moucari *et al* studied a group of patients whose BMI mean ± SD was 26 ± 3.8 kg/m^2.[144] Ziada *et al*'s study population had a BMI mean ± SD of 27.8 ± 1.5 kg/m^2 in insulin resistant cases compared to 21±2.6 kg/m^2 among non-insulin resistant cases.[131] As for De Souza *et al*, they also had similar results, their patients under study had a BMI mean ± SD of 26.1 ± 4.3 kg/m^2 and 29% of them had metabolic syndrome.[139] Moucari *et al*'s study population had a BMI mean ± SD of 23.7 ± 3.1kg/m^2 and metabolic syndrome was present in nearly half of their patients.[166] On the other hand Chehadah *et al*, in their study on non-diabetic CHC patients reported that 38% were obese (BMI >30 kg/m^2).[164] The difference in the results of the metabolic syndrome may be attributed to the strict selection criteria of patients candidate for treatment in the MOH national program and also may be due to difference in the exact definition of metabolic syndrome used for its diagnosis.

In this study, determining baseline HCV RNA showed that 22% of genotype 4 CHC patients had low level viremia, 43% had intermediate level viremia and 35% had high level viremia. Similarly Chehadah *et al* in their study on CHC patients showed that according to their basal viral load 29% had high level viremia while 71% had low level viremia.(164) Moucari *et al* studied CHC patients and found that 30% had high level viremia.(144) Khattab *et al* reported that 59.5% of their patients had low baseline viral load while 40.5% had high level viremia.(142) Moucari *et al* studied a group of CHC patients, 47.6% had high basal viral load and 52.4% had low baseline viremia.(166)

Liver biopsy specimens were examined for all 100 CHC patients included in this study. The degree of necroinflammatory activity and fibrosis was scored based on the Metavir system. Almost all studied patients had moderate to severe necroinflammatory activity (55% A1, 44% A2, 1% A3). Fibrosis was significant (F2-F4) in nearly half of them (F2: 45%, F3: 4% and none were F4). Other workers also reported their histopathological findings using the Metavir score. Similar to our results, Brandman *et al* reported that hepatic fibrosis was significant in 77% of cases and necroinflammation was severe in 52% of cases.(137) As for Moucari *et al,* the histopathological findings of their patients were as follows: necronflammation was severe in 30% and fibrosis was significant in 73%.(144) Likewise among the studied population of Moucari *et al,* severe necroinflammation was detected in 30% of cases and significant fibrosis in 55% of cases.(166) In Khattab *et al*'s series, the basal histopathological findings of the studied cases was as follows: significant fibrosis in 36.6%, necroinflammation: moderate in 68.6% of patients and severe in 31.3%.(142) Ziada *et al's* histopathological study of the liver biopsies of their patients showed that necroinflammation was severe in 33.3% and 25% of insulin resistant and non insulin resistant cases respectively while fibrosis was significant in 48% of IR cases compared to 24% among non-IR cases.(131) Patients with chronic hepatitis showing significant bridging fibrosis are better candidates for treatment than patients with cirrhosis and this explains that basal pretreatment liver biopsies of CHC patients included in most studies have fibrosis score by Metavir not reaching F4 (cirrhosis).

The relationship between hepatitis C virus (HCV), steatosis, and insulin resistance is genotype specific, and steatosis and insulin resistance are closely linked to the progression of liver disease in HCV infected patients. It is now accepted that in chronic hepatitis C, there can occur two types of steatosis, a "metabolic" steatosis, that is consequence of metabolic factors like alcohol consumption and risk factors of non alcoholic fatty liver (the most important ones being obesity, visceral fat and IR); and a viral steatosis that may result from a direct viral cytopathic effect. The former associates to genotype 1, 2 and 4. The latter associates to genotype 3 and does not relate to BMI or IR. (129) There are several identified mechanisms whereby HCV may alter lipid metabolism. Firstly, HCV core protein has been shown to directly inhibit the function of microsomal triglyceride transfer protein, a major regulator of hepatic assembly, and secretion of nascent triglyceride rich very low density lipoproteins (VLDL). The latter effect impairs the ability of hepatocytes to assemble and secret VLDL. Secondly, HCV core protein has been

observed to induce mitochondrial injury resulting in oxidative stress. Oxidative stress disturbs lipid peroxidation, thereby contributing to the development of steatosis. Finally, it has been illustrated that HCV has the ability to induce transcription of several genes involved in lipid metabolism in the liver. [129] In our study, mild and moderate steatosis were equally detected in genotype 4 CHC patients (each in 21.2% of patients). Steatosis was severe in 10.3% of patients and absent in 48.3% of patients. In Khattab *et al*'s study on CHC patients infected with genotype 4, steatosis was absent to mild in 78.6% of patients and severe in 21.3% of patients. [142] Others studying CHC patients infected with different genotypes reported various results. Steatosis was severe in 29% of Brandman *et al*'s patients [137], 26% of Moucari *et al*'s patients [144] and 31.2% of Moucari *et al*'s patients.[166]

The association between HCV infection and glucose abnormalities holds true if, instead of looking at the occurrence of overt T2D, one considers prediabetic conditions, such as insulin resistance (IR). Insulin resistance is defined as a condition in which higher than normal insulin levels are needed to achieve normal glucose metabolism or alternatively, normal insulin levels fail to achieve normal glucose metabolism. The causal relationship of HCV infection and IR development has been demonstrated by the increased prevalence of IR in chronic HCV infection. Whereas the overall prevalence of IR is 10%-25% of a population, the prevalence of IR in HCV infection reaches figures ranging between 30%-70%. Moreover, IR with HCV infection is increased at early stages of liver disease without liver fibrosis, and is on average significantly higher than that found in patients with chronic hepatitis B, matched for age and body mass index.[167] In this study, IR was detected in 31% of non-diabetic CHC patients (HOMA-IR > 3). Similarly, Moucari *et al* studied IR with the same HOMA-IR threshold discriminant, 32.4% of their non-diabetic CHC patients were insulin resistant. [166] As for Kim *et al*'s study, 35.7% of cases had HOMA-IR >3. [143] Other studies used a different threshold of HOMA-IR for diagnosis of IR in CHC patients (>2). In the studies of Moucari *et al*, Romero-Gomez *et al* and Ziada *et al*, 45.3%, 62% and 35% of their patients were insulin resistant.[131, 144, 168] De Souza *et al* considered patients with HOMA-IR > 2.5 as carriers of IR and accordingly 27% of their patients were insulin resistant.[139] Petta *et al* defined IR as having HOMA-IR > 2.7 and 35% of their patients were insulin resistant.[169] The difference in the prevalence of insulin resistance between these studies may be due to the difference in the size of the studied population as well as the difference in the definition of insulin resistance by HOMA-IR assessment model. Other factors that might cause these varying percentages could be related to patient age and HCV genotype and duration.

In the present study, pretreatment HOMA scores were categorized into three groups (<2, 2-4, >4). Significantly higher HOMA-IR values were found among the genotype 4 CHC patients in comparison with those among the HCV negative subjects (p=0.009). Similarly the median of HOMA-IR was significantly higher in the patient group (p=0.001). Likewise Park *et al* and Lonardo *et al* compared HOMA-IR in CHC patients and normal subjects and found a statistically significant difference (p<0.001). [170, 171] Lecube *et al* reported that the comparison between

hepatitis C infected cases and HCV negative controls had a statistical difference of p=0.01.[172] The difference in the results of the latter study may be attributed to the difference in the size of the studied HCV infected group.

In the current study, correlation between pre-treatment HOMA-IR and other variables was established using univariate analysis. Variables that achieved statistical significance were included in multiple linear regression analysis to evaluate the independent factors associated with HOMA-IR. In the univariate analysis, HOMA-IR was significantly associated with basal viral load and degree of fibrosis (p=0.029 and p=0.026 respectively). In the linear regression analysis, results revealed that baseline viral load remained the only independent variable associated with extent of IR as measured by HOMA score (p=0.001). Establishing a significant correlation between HOMA-IR and HCV-RNA levels demonstrates a direct role of viral replication in IR development. Similarly, Moucari *et al* found by univariate analysis that insulin resistance associated significantly with basal viral load (p=0.008) as well as by multiple logistic regression analysis (p=0.02).[166] In another study by Moucari *et al*, they also had similar results where the univariate analysis of insulin resistance showed statistically significant correlation with serum HCV RNA (p<0.001) and also by multiple logistic regression analysis (p=0.002).[144] On the other hand, the same correlational analysis in the Ziada *et al*'s study revealed that fibrosis and steatosis significantly affected the IR state among their patients.[131] Similarly, Khattab *et al* reported that high HOMA-IR correlated with fibrosis stage, steatosis, BMI and waist circumference while viral load was not correlated with HOMA-IR.[142] A large body of evidence demonstrates the association between IR and liver fibrosis. IR accelerates fibrosis progression via activation of stellate cells by hyperinsulinemia and increased levels of connective tissue growth factor, a cytokine involved in hepatic fibrogenesis, and subsequent accumulation of extracellular matrix. [173]

As regards the relationship between pre-treatment values of HOMA-IR and response to therapy in patients with genotype 4 chronic hepatitis C infection, this study concluded that having a lower baseline HOMA score lead to a favorable therapeutic outcome. There was a statistically significant difference in HOMA-IR of patients achieving cEVR and pEVR compared to that in non-responders (p=0.006). In concordance, Khattab *et al* stated that there is a highly significant relationship between insulin resistance and treatment response (p=<0.0001).[142] Similarly, Moucari *et al* concluded from their study that HOMA-IR <2 was associated with early virological response (p=<0.001) and also remained the independent predictor of sustained virological response by multiple logistic regression analysis (p=0.03).[144] Likewise, in a study carried out by Ziada *et al*, results showed that insulin resistance >2 had a significant impact on lack of SVR (p=<0.001). [131] On the contrary, Brandman *et al* studied the effect of IR on SVR but with multiple HCV genotypes and did not get significant results as regards the relation between both in any of the HCV genotypes.[137]

Virological responses during therapy, such as RVR and EVR, are now widely used for predicting final virological response because such treatment factors have even higher predictive value. In this series all patients that were followed after demonstrating EVR achieved ETR.

However it would be obvious that predictions made before initiating therapy could be even more desirable than those done during the therapeutic course. In order to identify baseline predictors that may help in attaining a favorable treatment response, we performed a univariate analysis of pretreatment variables. Results revealed that younger age, lower HOMA-IR scores, lower baseline HCV RNA level and lower grades of steatosis, were significantly associated with end of treatment response of our studied genotype 4 CHC patients. However, lower baseline viral load remained the only independent factor associated with end of treatment response in the multivariate logistic analysis. Similarly, Ziada *et al* univariate anlaysis of pretreatment variables showed that the older age, fibrosis >3, high viral load, as well as high HOMA-IR >2, were significantly associated with lack of SVR, whereas their multivariate logistic regression analysis showed that pretreatment HOMA-IR >2 was the only independent factor associated with lack of SVR.[131]. Also Khattab *et al* studied the pretreatment variables having significant impact on SVR and their results revealed that younger age, lower baseline viral load, lower HOMA-IR and less degree of fibrosis, were all significantly associated with SVR. As for their multivariate analysis, less degree of fibrosis, lower HOMA-IR and lower baseline viremia, were the independent factors associated with SVR in Egyptian genotype 4 CHC patients.[142] The controversy in the results of the multivariate analysis between the current study and that of others may be attributed to the difference in the size of the studied population and difference in the follow up of treatment response.

The current study also correlated the effect of successful treatment on the insulin resistance state in the selected chronic HCV patients, follow up of the complete early virologic responders till end of treatment showed decrease in HOMA-IR with statistical significance ($p=<0.001$). Another study by Brandman *et al* showed also similar results were they stated that after follow up of their patients, there was substantial decrease in insulin resistance level after 6 months from receiving antiviral therapy in comparison to those not receiving treatment.[137] Likewise Ziada *et al* follow up study of their patients showed significant decrease in their HOMA-IR scores after successful treatment ($p=0.009$) which is quite similar to our conclusion.[131]

In this study, 29 liver tissue sections from the selected cases were tested by immunohistochemistry for expression of insulin receptor substrate-1 to assess viral role in induction of insulin resistance state. Fourteen cases showed high level of IRS-1 expression with grades 2+ and 3+ while 15 cases had low level of expression zero and 1+ with no statistical significance. Kawaguchi *et al* demonstrated a two and three fold increase in intensities of IRS1 and IRS2 staining, respectively, after antiviral therapy. [141] They identified mechanisms for HCV-associated insulin resistance postulating that HCV core down regulates hepatic expression of IRS 1/2, and thus decreases downstream signaling effect of insulin on glucose uptake by cells. Almost half of the cases in our study showed low level of expression of IRS-1 which also supports the postulation of the direct role of the virus on insulin resistance mechanisms.[174]

The biological action of insulin involves modulation of a cascade of intracellular signaling molecules in response to circulating insulin binding to its cognate cell surface receptor. The insulin receptor is a tetrameric complex, consisting of two extracellular insulin-binding α-subunits and two b-subunits transversing the cell membrane; these subunits function as allosteric

enzymes, whereby the α-subunit inhibits the tyrosine kinase activity of the b-subunit. Furthermore, insulin binding promotes its receptor's autophosphorylation, which leads to tyrosine phosphorylation of the intracellular insulin receptor substrate (IRS)-1 and (IRS)-2, initiating a cascade of multifaceted events. Conversely, serine phosphorylation of the IRS proteins attenuates insulin signaling by decreasing insulin-stimulated tyrosine phosphorylation; this action acts as a negative feedback signal under normal physiologic conditions, providing a crosstalk mechanism between pathways that are not directly modulated by insulin but which can produce insulin resistance. Additional factors that suppress activation of IRS proteins have also been implicated in development of insulin resistance; these include the protein tyrosine phosphatases (PTPs), especially PTP1B, which dephosphorylate tyrosine residues on the insulin receptor or IRS-1/2, and the suppressor of cytokine signaling (SOCS) proteins, SOCS-1 and SOCS-3, which promote ubiquitin-mediated IRS-1 and IRS-2 degradation.(174)

The relationship between IR and HCV infection is complex and bidirectional; HCV induces steatosis, and the latter could also cause IR. In addition to inflammation, HCV proteins also play a role in the development of IR and oxidative stress, the two key pathways in the pathogenesis of non alcoholic fatty liver disease (NAFLD). On the other hand, insulin is an anabolic hormone and promotes hepatic lipogenesis, and inhibits lipolysis. Therefore, the initial step in HCV-related metabolic disorders remains unclear.(167)

Insulin resistance induces interferon resistance. IR is associated with a poor response to anti-viral treatment in patients with HCV infections, both for initial virological response and SVR. Although the reason for such association is largely unknown, several possibilities have been suggested. Obese HCV patients have lower chance of achieving SVR compared with non-obese patients. Obese HCV patients with steatosis are thought to have increased lipid droplets in hepatocytes, which can act as a functional barrier for the interaction between antiviral drugs and hepatocytes. Alternatively, lipids are important for HCV replication, and accumulation of hepatic lipid droplets may increase HCV replication and results in poor responses to anti-viral treatment. Obese people are known to have a poor lymphatic circulation; this could result in suboptimal serum levels of pegylated interferons (PEG-IFNs) and a reduced response to antivirals. Obesity may also affect the antiviral response by modulating the IFN signaling pathway, as studies showed that obese HCV patients had increased mRNA expression of SOCS-3 compared with normal controls.(167)

The diet and lifestyle recommendations for managing chronic hepatitis C are basically the same as those for obesity, diabetes and metabolic syndrome, reflecting the potential negative effects of metabolic factors on the clinical course of HCV infection. Exercise is a well-established behavioral modification that benefits metabolic disorders, and the molecular mechanism has been determined to involve exercise-stimulated glucose transport *via* activation of AMP-activated protein kinase (AMPK) in skeletal muscle. Since the AMPK pathway is independent of insulin signaling, exercise is effective for improving hyperglycemia without influence from an insulin resistant milieu. Although the precise impact of diet and lifestyle modifications on outcomes of HCV infection remain to be fully elucidated, appropriate diet and exercise

intervention can increase insulin sensitivity in HCV-infected patients, as well as improve early viral response to antiviral therapy.[174]

Although insulin resistance is strongly associated with resistance to IFN-based therapy in HCV-infected patients, the effect of insulin sensitizers on antiviral therapy seems to be restrictive.[174] In one study, administration of metformin was shown to improve the rate of sustained viral response (SVR) to peg-IFN plus ribavirin therapy in patients with HCV genotype 1 infection and insulin resistance;[175] however, another study indicated that the metformin effect was limited to female patients.[168] Administration of pioglitazone was similarly reported to improve viral response to peg-IFN plus ribavirin therapy in patients with HCV genotype 4 and insulin resistance,[176] but shown to provide no benefit to patients with HCV genotype 1 and insulin resistance.[177] In contrast, several studies have detected a harmful effect of sulfonylurea or insulin on HCC incidence in HCV-infected patients; however, the metformin appeared to provide a benefit in regard to this disease outcome.[178, 179]

Insulin resistance has emerged as an important prognostic factor for the clinical course of HCV infection, due to its association with resistance to antiviral therapy, progression of hepatic fibrosis,[180] development of hepatocellular carcinoma (HCC), and poor quality of life. In addition, insulin resistance, as well as oxidative stress, has been shown to contribute to the HCV-related disruptions in host metabolic factors, particularly lipids and iron. Visceral obesity has been shown to enhance HCV-induced insulin resistance, and HCV infection in patients with both obesity and diabetes mellitus has been reported to strongly promote the development of HCC. Thus, synergistic effects of viral and metabolic factors are hypothesized to contribute to hepatocarcinogenesis.[174]

Considering HCV infection on the causal side of insulin resistance may have important implications. From the management point of view; should patients with CHC be monitored regularly for IR? A practical and also well-accepted method of measuring IR is the HOMA-IR (homeostasis model assessment of IR) which-being a noninvasive, non expensive test–can be implemented easily in routine clinical practice.

Hepatitis C promotes insulin resistance, and IR produces interferon resistance, steatosis, and fibrosis progression. IR is a potentially modifiable host-related factor that accelerates liver fibrogenesis, so future studies are needed to assess whether the IR control strategy is able to reduce HCV-induced histological injury when metabolic parameters in HCV-positive patients are normalized.

There is a growing interest in the relationship between hepatitis C virus and host. These results suggested the possible value of evaluating IR for predicting treatment response in HCV-4-infected patients, the fixed standard therapy of 48 weeks offered by the Bureau of National Health Insurance in Egypt should consider; given the limitations of financial resources, tailoring the treatment duration to be optimal, when high HOMA-IR is found in these patients. Pretreatment measurement of HOMA-IR, in combination with tests of HCV RNA load at the start of therapy and during treatment, may be used as determinants for selecting regimens in

CHC patients. Moreover, this study supports the use of strategies to modify IR before or during combination therapy as a feasible approach for enhancing the likelihood of treatment response, especially for HCV-4 patients.

SUMMARY

Estimates place the number of HCV infected individuals at approximately 170 million, representing nearly 3% of the world's population. Viral hepatitis is the most significant public health problem facing Egypt today. HCV prevalence rates in the general population are estimated at between 10% and 15% in rural areas, with some age groups suffering from prevalence rates of up to 50%. Since 2006, Egypt has made great progress in the management of viral hepatitis in establishing a National Committee for the Control of Viral Hepatitis with 23 affiliated viral hepatitis treatment units distributed all over the country as a part of Viral Hepatitis National Treatment Program launched in 2008. Between 2006 and 2012, more than 220 000 HCV patients were treated in National Treatment Centers and HIO centers. Currently, Egyptians being treated for HCV receive 48 weekly subcutaneous doses of pegylated interferon with twice daily doses of ribavirin, though new treatment regimen with sofosbuvir is on its way for implementation.

The association between T2DM and CHC was first reported in 1994 by Allison et al, who observed that the prevalence of T2DM was significantly higher in those with HCV-related cirrhosis than those with cirrhosis resulting from other liver diseases. Evidence showing a direct diabetogenic effect of HCV *per se* was studied. Also immunologic effect is known, through induction of a Th1 lymphocyte immune-mediated response which leads to activation of the tumor necrosis factor (TNF)-α and elevation of interleukin-6 levels. Insulin carries its biological effects through phosphorylation of the substrate of the insulin receptor 1 (IRS-1) and 2 (IRS-2). A high TNF-α level was considered to be one of the bases of insulin resistance (IR), which act by disturbing tyrosine phosphorylation of insulin receptor substrate (IRS)-1, a central molecule of the insulin-signaling cascade.

The association between HCV and IR has significant clinical consequences. Mounting evidence indicates that HCV-associated insulin resistance may cause accelerated fibrogenesis, reduced response to IFN-based therapy and hepatocellular carcinoma. Increased levels of IR are associated with reduced rates of initial virological response as well as sustained virological response in CHC patients treated with a combination of pegylated IFN-α and ribavirin. This implies that pre-diabetic conditions as insulin resistance should be warranted, the Homeostatic Model Assessment (HOMA), offers an easy way for its estimation.

Our aim was to evaluate the prevalence of insulin resistance in Egyptian patients infected with chronic hepatitis C virus genotype 4, to assess factors associated with insulin resistance in those patients and to test the impact of insulin resistance on treatment outcomes.

The prevalence study of their HOMA-IR was 31% >3.0. The median of the BMI of the 100 CHC patients included in the study was 27.60 with mean ± SD 27.06 ± 3.44. Metabolic syndrome was present in 15% of them. As for the immunohistochemical studies for IRS-1 of 29 selected liver sections of these patients, 15 cases showed weak staining of 10-50% or less of hepatocytes and 14 cases showed strong staining of 50% or more of hepatocytes.

The correlational studies between insulin resistance and age, BMI, basal viral load, lipid profile, fibrosis staging and steatosis grading, showed statistically significant difference between HOMA-IR and basal viral load and fibrosis stage. When the data were analyzed by multivariate linear regression, results suggested that basal viral load remained the only independent factor associated with elevated HOMA-IR levels (p=0.001). As for the univariate analysis of pretreatment variables affecting treatment outcome, this study revealed that the younger age, lower HOMA-IR scores, lower baseline HCV RNA level and lower grades of steatosis, were significantly associated with end of treatment response of our studied CHC patients. The multivariate logistic analysis showed that the lower baseline viral load remained the only independent factor associated with end of treatment response.

These results show that chronic hepatitis C patients with genotype 4 have high prevalence of insulin resistance. It also shows that patients with insulin resistance are more liable to treatment failure with peg-interferon alpha plus ribavirin. It also shows that the insulin resistance state improves with successful treatment.

CONCLUSIONS

- This study shows that there is a high prevalence of insulin resistance HOMA-IR >3 among chronic Hepatitis C patients with genotype 4 (31%).
- Few patients in this study fulfilled the definition of metabolic syndrome (15 patients).
- Most of our patients were F1-F2, A1-A2 Metavir stage and more than half showed steatosis.
- Immunohistochemical study of IRS-1 showed that almost half (15 cases) of the studied CHC patients showed low level of IRS-1 expression in liver tissue sections.
- The univariate analysis of factors affecting response to treatment showed that the younger the age of the patient, lower stage of fibrosis, lower basal viral load and lower HOMA-IR, all had significant association with complete virological response to treatment.
- The multivariate analysis of the pretreatment variables affecting end of treatment response, showed that the pretreatment baseline viral load remained the only independent predictor.
- The univariate analysis of factors affecting insulin resistance showed that basal viral load and stage of fibrosis were significantly associated with HOMA-IR score.
- The multivariate analysis of factors affecting HOMA-IR showed that the baseline viral load remained the only independent predictor of insulin resistance.
- Follow up of the studied cases showed that there was a statistically significant decline in HOMA-IR of patients who achieved complete early virological response denoting the viral role in development of insulin resistance.