# DISCUSSION

Hepatitis C virus (HCV) infection is a major health problem, Worldwide, it is estimated that 170-200 million people are living with chronic hepatitis C infection (~3% of the world's population), that it infects 3-4 million people per year, >10% of these people will develop liver cirrhosis or cancer over time and that more than 350,000 people die from hepatitis C related diseases each year [9]. Egypt has one of the highest prevalence rates of hepatitis C virus (HCV) infection in the world. The HCV epidemic appears to have been initiated by vigorous public-health campaigns using intravenous tartar emetic from the 1950s until 1982 to eradicate schistosomiasis [239]. This iatrogenic mode of infection has now resulted in a high incidence of hepatic morbidity and mortality from the late complications of HCV infection, such as chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC)[240,241].Among the six major HCV genotypes found worldwide [242], genotype 4 is the most predominant in Egypt [243,244] with 4a as the dominant subtype [245].

Treatment of HCV using combination of pegylated interferon (PEG-IFN) plus ribavirin fails in about 50% of the patients and is physically and economically demanding. Thus, it is highly important to understand the mechanisms of non-response to overcome it and to identify factors that can help to predict the chance of each patient to respond to the treatment. Different elements are associated with non-response: (i) viral factors, (ii) host factors and (iii) molecular mechanisms induced by HCV proteins to inhibit the IFN signaling pathway [197].

Accordingly, the present study was aimed to investigate and throw more lights on the effect of some of viral and host factors on the response to treatment, Peg-IFN-α/RBV, in HCV patients. The study was carried out on thirty apparently healthy subjects as well as eighty eight HCV infected patients. In both groups liver and kidney function tests, lipid profile, insulin resistance and complete blood picture were assessed.

The initial diagnosis of liver diseases is carried out by routine liver function tests like serum level of ALT, AST, ALP, bilirubin, albumin, globulin, and so forth. The levels of these enzymes or proteins are altered during hepatic injuries, hepatitis B or C infection, liver cirrhosis, and Hepatocellular Carcinoma (HCC) [246]. Elevated aminotransferases levels act as indicators of liver cell injury [247,248] and are usually predominant in liver cirrhosis with increased ALT levels [249]. The pattern of the aminotransferase elevation can be helpful diagnostically [250]. Usually in hepatitis C virus infection the levels of both ALT and AST are examined routinely in the patient's serum however, in some cases; the level of these enzymes remains unaltered or under normal value [251].

The ALT and AST are also important biological markers that are widely used for liver diseases. All types of hepatitis and cirrhosis have been reported to cause liver damage that can lead to elevations in the serum ALT and AST activities. That were a significant increase in ALT, AST and ALP activities in patients with HBV and HCV, damaged liver cells may be the result of increase these enzymes activities[252]. Ijaz et al, 2011[253], reported that in serum markers bilirubin, ALP and ALT were significantly high in HCV patients with genotype 4. It should be noted that high bilirubin level is usually associated with liver metastases and liver tumor involvement leading to hepatocellular carcinoma and liver cirrhosis by active or non- active HCV or HBV [253]. In accordance with

aforementioned studies, the data of the present study revealed a significant increase in the serum activities of ALT, AST and ALP in patients with HCV infection.

However, the data of the present study revealed a significant reduction in serum albumin levels of HCV patients. A low serum albumin concentration indicates poor liver function. Decreased serum albumin levels are not seen in acute liver failure because it takes several weeks of impaired albumin production until the serum albumin level drops. The most common reason for a low albumin is chronic liver failure caused by cirrhosis. The serum albumin concentration is usually normal in chronic liver disease, until cirrhosis and significant liver damage develops. In advanced liver disease, the serum albumin level may be less than 3.5 g/dl. The albumin level is clinically important as a predictive factor for patients with liver cirrhosis, because decreased serum albumin levels cause ascites and edema [254].

On the other hand, interactions between chronic HCV infection and lipid metabolism have been described in several studies [255-259].Some studies have reported a higher prevalence of hypercholesterolemia and low LDL levels in HCV-infected patients compared to control groups [256,258,259]. Other studies showed decrease levels of triglycerides among chronic HCV patients [260], Although changed serum lipid is commonly found in patients with chronic liver disease of any etiology, the relationship between HCV and lipid metabolism seems to be more specific: binding of HCV particles to human high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL) has been described, Thomson et al, 1993 [255]. Moreover, the LDL receptors could permit the entry of HCV into hepatocytes [261,262].

Also, HCV replication could decrease intrahepatic cholesterol synthesis. Thus, the decrease in available intracellular cholesterol may lead to an increase in LDL receptors and intrahepatic LDL. This increase in LDL uptake may account for the decreased serum LDL levels in HCV infection [262]. Nashaat, 2010 [263], has investigated the effect of chronic HCV infection on the lipid profile among Egyptian HCV patients. In his study, and in agreement with the results of the present study, he demonstrated that HCV patients had significantly lower total cholesterol and LDL levels than the uninfected control group. These results agree with several studies [258-260,264] and Corey et al, 2009 [265] who observed that frequency of hypo-cholesterolemia in non-cirrhotic HCV-infected patients was five times higher than in their reference population. Also, in agreement with Nashaat, 2010 and Corey et al, 2009 [265], the results of the present study revealed that HDL levels were not statistically significant between the HCV patients and apparently healthy subjects. The mechanisms by which HCV infection may lower total cholesterol are still speculative and may include, among others, the binding of HCV particles to HDL, LDL and VLDL [255] and the impaired hepatocyte assembly of VLDL through inhibition of the microsomal transfer proteins [266] or through depletion of the intra-hepatocyte intermediate fatty acids as mevalonic acids and geranylgeranyl lipid required for HCV RNA replication and formation of HCV core proteins [267].

In vivo and in vitro data suggest that statins, the widely used cholesterol-lowering drugs, may inhibit HCV RNA replication by depletion of geranylgeranyl lipid [268]. Interestingly, the triglycerides levels in HCV patients are controversial. Several studies have postulated the significant decrease the triglycerides level [263] in HCV while other studies have demonstrated the comparable levels of triglycerides in HCV patients with that

in the healthy subjects [265]. In agreement with results of the present study, Mustafa et al, 2012 [269], have reported that serum triglycerides level was greater in HCV patients than that in healthy subjects. Recently, it has suggested that serum triglyceride may have an important role in viral replication and therapies directed at lowering triglyceride levels may enhance the efficacy of current antiviral treatment regimen [270].

Meanwhile, the data of the present study revealed that the fasting blood sugar level in HCV patients was significantly higher than that in apparently healthy subjects. HCV infection promotes the expression of gluconeogenic genes namely, glucose 6 phosphatase and phosphoenolpyruvate carboxykinase 2 resulting in increased glucose production and enhanced insulin resistance [271,272]. HCV also down regulates the expression of glucose transporter-4, which is necessary for uptake of glucose. This results in a decreased glucose uptake and increased plasma glucose, leading to development of insulin resistance [272].

It should be noted that the results of the present study revealed that fasting insulin level in HCV patients was significantly elevated when compared to that in apparently healthy subjects. Fukui et al, 2002 [273], have reported a significant elevation of fasting insulin level in HCV patients. Insulin resistance and subsequent hyperinsulinemia are highly associated with fatty liver disease and are important factors for the progression of fibrosis in CHC. High levels of insulin and glucose could promote fibrogenesis by stimulating release of connective tissue growth factor from hepatic stellate cells [274].

In the current study, the data showed that HCV patients have a significant reduction in the count of WBCs and platelets as well as a significant decrease in the hemoglobin level. Preliminary data suggest that the infection itself can induce autoimmune hemolytic anemia, leukopenia, and thrombocytopenia [275,276].These complications can influence HCV treatment and adherence, which could compromise outcomes. Although no approved treatments for HCV-related hematologic complications exist, this review will summarize the pharmacology, risks, and benefits of the investigational use of hematopoietic growth factors for treating such complications [277].

In patients group, the response to Peg-IFN-α/RBV was examined after 24 weeks by qualitative RT-PCR. The results showed that 64% of the patients responded to the treatment while 36% of the patients did not respond the standard of care treatment.

In agreement with previous reports, the data of this study showed that there is no significant difference in AST and ALT level between responders and non-responders HCV patients [278,279].

The data of the present study revealed that the serum albumin level in responder was higher than that in non-responder HCV patients. Assem M, et al. has reported the same observations in responder HCV patients with genotype 4[280]. Faisal, et al, 2013 [279], have reported is no significant difference in serum albumin between responders and non-responders. However, it was reported that serum albumin < 3.9 g/dl is significantly associated with a non-virological response [281].

Also, the data showed that the total and direct bilirubin serum levels in responder HCV patients were significantly lower than that in non-responder HCV patients. Hosogaya et al, 2006 [282], reported that low total bilirubin level is significantly associated with SVR.

As previously mentioned, the main factors influencing the efficacy of HCV antiviral treatments are divided into two categories; viral and host-related. The viral category includes the HCV genotype and baseline viral load [283]. The later, is an important determinant of treatment response, the lower the viral load the better the chance of eradicating the hepatitis C virus. In contrast, the data of the present study, despite the lack of statistical significance, showed that responders had a higher baseline viral load than non-responders. Domagalski et al, 2013 [284], have reported that the baseline viral load in responder was higher than that in non-responders HCV patients. These results may point to the role of other viral/host factors in predicting overall virological response.

On the other hand, host factors that are responsible for responsiveness to HCV therapy with Peg-IFN-α/RBV include age, sex, race، stage of fibrosis, GGT level, body mass-index (BMI), HCV genotype, and viral load, as well as virus variability have been studied [285,286].

Patient age is associated with responsiveness to Peg-IFN-α/RBV therapy in chronic HCV infection. Generally, it is believed that younger individuals (usually < 40 years of age) respond better to IFN-α treatment than older person s[287,288]. However, the results of the present study showed that mean average age of responders was not significantly different from that of non-responders.

The data of the present study revealed a significant elevation in the mean GGT activity level in non-responder HCV patients when compared to that in responder HCV patients. Similarly, Brjalin et al, 2013 [289], have reported that the mean GGT level significantly lower in the SVR group than in the non-SVR group. Low GGT levels were found to be an independent predictor of both RVR [290] and SVR [291,292] in various cohorts of HCV-monoinfected patients. In addition, it has been shown that GGT elevation is the strongest predictor of virologic non-response in Hepatitis C Virus genotype 1(HCV-GT 1) patients [293]. Moreover, it has been concluded that GGT is an independent predictor of both virological response and clinical outcomes among patients with advanced liver disease due to HCV Wright [294]. In agreement with previously mentioned studies the data of the present study revealed that GGT is independent predictor of virological response. Also, patients with low GGT activity level have approximately an 88% higher chance of developing a response to therapy compared with patients with elevated activity of serum GGT.

It has been suggested that obesity, only as defined by a BMI greater than 30 $kg/m^2$, is a risk factor for non-response to antiviral therapy independent of genotype and the presence of cirrhosis on pretreatment liver biopsy in patients with chronic hepatitis C. Obese patients as judged by their BMI, independent of genotype and cirrhosis, had approximately an 80% lower chance of a sustained response to therapy compared with normal or overweight patients [295].

The data of the current study showed that the mean value BMI of non-responder HCV patients was significantly higher than that in responder HCV patients. Also, the data showed that obesity (BMI $\geq$ 30 $kg/m^2$) was observed in 19.4% and 3.5% of non-responder and responder HCV patients, respectively. Moreover, the data of the current study demonstrated that obese patients as judged by their BMI had approximately an 85% lower chance of developing a response to therapy compared with normal or overweight patients.

BMI should be checked regularly during the period of therapy since one unit increase in baseline BMI Z score was associated with a 12% decrease in the probability of SVR [296].

Several studies have reported association between insulin resistance (IR) and chronic HCV infection especially with genotype 1 and 4[297,298].The association of IR and CHC ranged between 30% and 70%, the higher association is with genotype 1 and 4[299]. In consistence with these observation, the current study reports that almost 50% of the HCV patients have IR (HOMA-IR ≥ 2). Also, the data showed that the mean concentration level of fasting insulin was significantly higher in non-responder HCV patients when compared to that in responder HCV patients. Several studies have demonstrated that IR has impact on the natural history of the disease and treatment outcomes. IR is associated with a poor response to anti-viral treatment in patients with HCV infections, both for initial virological response [300-301] and sustained virological response (SVR) [302,303]. This negative association has been reported to occur both in patients infected with the genotype 1[302,304] and in those with genotypes 2 and 3[305].

Also, a link between genotype 4 and IR has been elucidated the in Egyptian population [280]. Accordingly, clinical trials of insulin-sensitizing drugs have been proposed to improve treatment response [306]. In the present study, the mean level of IR in non-responder HCV patients was higher than that in responder HCV patients without reaching a significant level. Similarly, Del Campo et al, 2013 [307], have reported similar results where no significant difference in IR level was observed between SVR and Non SVR. However, Deltenre et al , 2011 [308], in their a meta-analysis study, have reported that on considering only studies using the same cutoff value of 2 to define IR, a 22% decrease in SVR rates was still found. They also stated that this cutoff (2) is a robust negative predictive factor for SVR. In these aspects, the results of the present study revealed a 21.5% decrease in response rate.

The mechanisms by which IR interferes with the response to antiviral treatment are manifold. Experimental data have suggested that IR-associated hyper insulinemia may interfere with the IFN pathway [309]. It has been shown that insulin is able to increase HCV RNA production in replicon systems and to diminish expression of proteins involved in interferon signaling [309]. Overexpression of suppressors of cytokine signaling, especially SOCS-3, in insulin-resistant patients may be another mechanism implicated in reduced SVR rates. Interferon signaling is down regulated by SOCS-3 and in vitro studies have shown that SOCS is able to promote degradation of the insulin receptor substrate (IRS)-1[310]. Levels of SOCS-3 have been reported to be increased in cells expressing the HCV core protein as well as in the liver of chronic hepatitis C patients not responding to antiviral therapy [311]. Generally, it was suggested that the activation of SOCS family members may be a mechanism common to all major HCV genotypes [312].

However, these results have not been confirmed by others and should be tempered by the fact that the role of systemic low-level inflammation may be predominant and that chronic hepatitis C is associated with peripheral rather than hepatic IR [313,314]. Accordingly, IR and the features of the metabolic syndrome should be assessed in patients with CHC, since IR is a risk factor for fibrosis progression. Antiviral treatment of the patients at risk is recommended as soon as possible, while specific pharmaceutical treatment of insulin resistance is not yet established. In this regard, the identification of

drug targets in key positions of HCV induced IR development is needed to selectively improve treatment outcome in these patients and thus prevent fibrosis progression [315].

Chronic hepatitis C infection progresses to fibrosis and in 20%–30% of cases leads to liver cirrhosis with the risk of hepatocellular carcinoma (HCC) (4%) [316]. Gamail et al, 2013 [317], have reported that stage of fibrosis in patients with HCV genotype 4 is one of the most important predictors of EVR, as the higher the stage of fibrosis, the lower the achievement of a complete EVR. Their results were also reported by Torres et al, 2010[318], who demonstrated, that one of the independent factors associated with a complete EVR was the non-cirrhotic status of the patients HCV I at baseline. De Careaga et al, 2006 [319], reported that patients with hepatitis C and cirrhosis have lower rates of sustained responses even with the absence of cirrhosis, the degree of response to treatment decreases with the increase of stage of fibrosis.

It has been demonstrated that the presence of liver steatosis and significant fibrosis, which are highly prevalent in chronic HCV infection, also significantly impairs the chance for SVR, with rates of 15–40% according to the degree of steatosis and fibrosis [320-324]. The data of the present study are in agreement with and confirm the previously mentioned observations. Also, the data of the present study showed elevated stages of fibrosis reduces the chance for virological response with rate of 17%. Thus, presence of advanced fibrosis was a strong predictor of non response when compared with those who gained early virological response. This finding also goes in line with previous Egyptian studies on HCV patients with genotype 4 and declared that advanced fibrosis was associated with treatment failure [325].

Explanations for the influence of liver fibrosis are varied: 1) the influence of liver fibrosis could be attributed to the higher number of secondary effects detected in these patients [324,326,327], an alternative explanation is that lower percentages of HCV infected hepatocytes and hepatocyte infection rate are predictors of SVR [328]. Interestingly, the absence of significant liver fibrosis was a predictive parameter of SVR mainly in those patients without RVR. This has a practical consequence: when RVR is used to identify patients to be treated only with Peg-IFN and RBV, the presence or absence of significant liver fibrosis is not a definitive factor in the decision between dual (only Peg-IFN plus RBV) or triple therapy (adding telaprevir or boceprevir) [329].

Currently, candidate gene approaches had been implemented to discover the host factors associated with the HCV treatment response [330]. Several favorable genotypes significantly predicting higher sustained virological response rates including IL-28 CCrs12979860 irrespective of the race have been reported [331].The data of the present study revealed that The frequency of the IL-28-rs12979860 genotype showed that more than half of the HCV patients CT (58 %), followed by CC (26 %) then TT (16 %). The same frequency order of IL-28B rs12979860 genotype was previously reported [332].

Also, the data of the present study revealed that the frequency of IL-28-rs12979860 CC genotype in responder patients (91.3 %) higher than in non-responder patients (8.7 %). Previously, several studies have reported elevated frequency of IL-28-rs12979860 C/C genotype in responder patients in relation to that in non responder patients [332,333]. Meanwhile, the data of the present study revealed a significant correlation between CC genotype and response to Peg-IFN-α/RBV. The response rates were almost 91 %, 57 % and 50 % for genotypes CC, CT and TT, respectively. This in agreement with previous

studies [332-335] where the high rates with response was observed in patients with CC genotype.

The exact biological pathways underlining the IL28B gene SNP association with treatment response and viral clearance remain unknown. Host innate immune mechanisms including IFN-λ, a direct product of the IL28B gene, control viral infection [336]. Initial binding of IFN-λs to its receptor is followed by several events that end with the induction of interferon-stimulating genes (ISGs) [337]. It is speculated that this mechanism suppresses viral infection. Moreover, IFN-λ has been shown to block HCV replication in human hepatocytes in vitro [337]. The role of IL-28B variants in relation to INF-λ3 expression could be explained by a number of possibilities:

- IL-28B SNP may be a marker of another DNA sequence that modifies the gene expression. Actually, the protective CC genotype of rs12979860 is strongly associated with a non-synonymous IL-28B mutation (rs8103142). Since this mutation is distant from the receptor binding site, it has no effect on INF-λ3 antiviral activity [338].
- The upstream location of the rs12979860 SNP in IL-28B gene may correlate with the regulation of IL- 28B transcription [339].
- Alternatively, it can act indirectly through modification of a transcription factor binding site [340].
- Finally, IL28B variants might cause an abnormal expression of endogenous IFN-λ3 (non-, weak-, or hyper-functioning variants). This might alter the host response to antiviral therapy by negative feedback [340].

On the other hand, the impact of IL28B rs12979860 CC genotype on metabolic profile has reported. Several studies have reported that patients with the CC polymorphism in IL28B had higher levels of total and low-density lipoprotein cholesterol [341,342]. These also go with results of present study. Li et al, 2010 [343], have shown an association between rs12979860 genotype and host serum lipid levels, suggesting a relationship between endogenous IFN response and lipids. They hypothesize that the IFN-lambda rs12979860 CC responder genotype, which was associated with both increased likelihood of treatment response and higher LDL cholesterol levels in the studied cohort, is associated with lower IFN-lambda activity or lower intrahepatic IFN signaling gene expression. It has been suggested that the observed associations are directly related to hepatitis C virus–host interactions instead of a direct effect of this locus on lipid metabolism [342]. Thus, the results of the present study may confirm this suggestion which was based on the observation that genotype CC of IL28b was more often seen in genotype 3 and non-infected patients than in genotypes 1 and 4 [344].

Interestingly, the results of the present study showed that high frequencies of elevated stages of fibrosis and serum GGT activity were observed in non-responders HCV patients with non-CC IL28B polymorphism. It has been reported that baseline GGT was associated with different host factor including interleukin (IL-28B) rs12979860 CT and TT genotypes and numerous markers of liver disease injury and severity [345].

IL28B rs12979860 TT-genotype was in 629 Italian patients an independent predictor of a higher Ishak staging score [346]. Fabris et al 2012 [347], analyzed retrospectively in a longitudinal study the fibrosis progression in Hepatitis C GT 1–4 patients. Over a period of 10 years Non-CC carriers with a serum cholesterol ≤175 mg/dL had fibrosis progression more frequently. Both factors were independently predictors for fibrosis progression [347]. Nevertheless, to determine the role of IL28B in fibrosis progression for clinical decision making further studies are needed.

**In conclusion**, as interferon responsiveness is still a main clinical problem in the treatment of HCV, the present study is an attempt to through more lights on the impact of viral and several host factors on the response to standard care of treatment of HCV. However, the precise prediction which patient will respond to this therapy is very important, both from the point of the patient care and of the costs. There are both host and viral factors which can significantly predict the probable treatment outcome of HCV patients. HCV genotype other than 1 is the most important predictor of SVR. A number of host factors including SNPs of interferons IL28A, IL28B, IL29, interferon-γ, Monoclonal B-Cell Lymphocytosis (MBL), IL −10, IL-18, Cytotoxic T-lymphocyte-associated protein 4 (CTLA4), Tumor necrosis factor (TNF)-related a apoptosis inducing ligand (TRAIL), Transforming growth factor-beta (TGF-β), Myxovirus-resistant 1(MX1), Osteopontin, low molecular mass polypeptide 7 (LMP7), genes encoding active The 2'-5'oligoadenylate synthetase (OAS) enzymes (OAS1 genes), insulin resistance, obesity and ethnicity, have been found to modulate the treatment response. There is still a struggle for discovering new direct-acting inhibitors of HCV that will be used in combination with interferon or without the application of interferon, so further future studies of factors that may predict the treatment outcome of combinational therapies are required.

# SUMMARY AND CONCLUSION

Egypt has one of the highest prevalence rates of hepatitis C virus (HCV) infection in the world. The HCV epidemic appears to have been initiated by vigorous public-health campaigns using intravenous tartar emetic from the 1950s until 1982 to eradicate schistosomiasis. This iatrogenic mode of infection has resulted in a high incidence of hepatic morbidity and mortality from the late complications of HCV infection, such as chronic hepatitis, cirrhosis and hepatocellular carcinoma. Among the six major HCV genotypes found worldwide, genotype 4 is the most predominant in Egypt with 4a as the dominant subtype.

On the other hand, treatment of HCV using combination of pegylated interferon (PEG-IFN) plus ribavirin fails in about 50% of the patients and is physically and economically demanding. Thus, it is highly important to understand the mechanisms of non-response to overcome it and to identify factors that can help to predict the chance of each patient to respond to the treatment. Different elements are associated with non-response: (i) viral factors, (ii) host factors and (iii) molecular mechanisms induced by HCV proteins to inhibit the IFN signaling pathway. Therefore, the present research work aimed to investigate and throw more lights on the effect of some of viral and host factors on the response to treatment, Peg-IFN-α/RBV, in HCV patients.

The study was carried out on thirty apparently healthy subjects as well as eighty eight HCV infected patients. Liver and kidney function tests, lipid profile, insulin resistance and complete blood picture were assessed in both groups.

In HCV patients, serum bilirubin, ALP and ALT were significantly higher than whereas, serum albumin was significantly lower than in apparently healthy subjects. These results may reflect liver damage due to HCV infection.

Also, in the present study, the interactions between chronic HCV infection and lipid metabolism have been investigated. In HCV patients, the data revealed a significant elevation in the TG serum level accompanied by a significant reduction of total cholesterol and LDL-cholesterol serum levels. These observations may throw more lights on the role of lipids in the entry and replication of HCV in hepatocytes.

Meanwhile, the data of the present study revealed that the fasting blood sugar and insulin levels in HCV patients were significantly higher than that in apparently healthy subjects. High levels of insulin and glucose could promote fibrogenesis by stimulating release of connective tissue growth factor from hepatic stellate cells.

It should be noted that the results showed that 64% of the patients responded to the treatment while 36% of the patients did not respond the standard of care treatment. The main factors influencing the efficacy of HCV antiviral treatments are divided into two categories; viral and host-related. The data of the present study, despite the lack of statistical significance, showed that responders had a higher baseline viral load than non-responders. These results may point to the role of other viral/host factors in predicting overall virological response. However, the results of the present study showed that mean average age of responders was not significantly different from that of non-responders.

Meanwhile, the data of the present study revealed that GGT is independent predictor of virological response. HCV patients with low GGT activity level have approximately an 88% higher chance of developing a response to therapy compared with patients with elevated activity of serum GGT.

Also, the data of the current study demonstrated that obese patients as judged by their BMI had approximately an 85% lower chance of developing a response to therapy compared with normal or overweight patients

Moreover, it has been reported that insulin resistance (IR) is associated with a poor response to anti-viral treatment in patients with HCV infections. Previously, it has been stated that IR with cutoff (2) is a robust negative predictive factor for SVR. In these aspects, the results of the present study revealed a 21.5% decrease in response rate.

It has been demonstrated that the presence of liver steatosis and significant fibrosis, which are highly prevalent in chronic HCV infection, also significantly impairs the chance for SVR. The data of the present study are in agreement with and confirm the previously mentioned observations. Also, the data of the present study showed elevated stages of fibrosis that reduce the chance for virological response with rate of 17%. Thus, presence of advanced fibrosis was a strong predictor of non-response when compared with those who gained early virological response. This finding also goes in line with previous Egyptian studies on HCV patients with genotype 4 and declared that advanced fibrosis was associated with treatment failure.

Currently, candidate gene approaches had been implemented to discover the host factors associated with the HCV treatment response. Several favorable genotypes significantly predicting higher sustained virological response rates including IL-28 CCrs12979860 irrespective of the race have been reported. The data of the present study revealed that the frequency of IL-28-rs12979860 CC genotype in responder patients (91.3 %) higher than in non-responder patients (8.7 %). Also, the data revealed a significant correlation between CC genotype and response to Peg-IFN-α/RBV. The response rates were almost 91 %, 57 % and 50 % for genotypes CC, CT and TT, respectively.

On the other hand, the impact of IL28B rs12979860 CC genotype on metabolic profile has reported. Several studies have reported that patients with the CC polymorphism in IL28B had higher levels of total and low-density lipoprotein cholesterol. These also go with results of present study. The results of the present study may confirm the suggestion that the observed associations are directly related to hepatitis C virus–host interactions instead of a direct effect of this locus on lipid metabolism. This suggestion was based on the observation that genotype CC of IL28b was more often seen in genotype 3 and non-infected patients than in genotypes 1 and 4.

Interestingly, the results of the present study showed that high frequencies of elevated stages of fibrosis and serum GGT activity were observed in non-responders HCV patients with non-CC IL28B polymorphism. It has been reported that baseline GGT was associated with different host factor including interleukin (IL) 28B rs12979860 CT and TT genotypes and numerous markers of liver disease injury and severity.

In **conclusion**, the present study is an attempt to through more lights on the impact of viral and several host factors on the response to standard care of treatment of HCV. The data of the present study revealed that GGT, BMI, IR and fibrosis are important independent predictors of virological response.