

REVIEW

The effects and underlying mechanism of interferon therapy on body weight and body composition

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Abstract: Body weight changes in HCV patients on interferon therapy are well documented. However, the underlying mechanism involved in these changes is poorly understood and rarely reported. The main objectives of this review are to 1) discuss changes in body weight and other compartments of body composition, particularly, body fat, and 2) to discuss the underlying mechanism for these changes. The literature review suggests weight loss (12-29%) as a function of interferon therapy is common, affecting up to 90% of HCV patients. Whilst, loss in weight means proportionate loss in other body compartments (lean body mass and body fat, in particular) data on changes in segmented body composition are fragmentary. The possible mechanisms underlying weight loss or changes in other body composition have been reported and these include suppressed appetite due to induction of TNF by IFN, a decrease in serum leptin level, and importantly mitochondrial damage induced by the therapy. It is, therefore, suggested that close monitoring of chronic HCV patients receiving PEG-IFN and/or ribavirin for side effects of these drugs, particularly those related to weight loss, is vitally important from clinical point of view.

Keywords: HCV, interferon, weight loss, body composition, mitochondrial damage.

INTRODUCTION

Hepatitis C treatment is improved dramatically after the introduction of pegylated interferon (PEG IFN) and/or ribavirin therapy and it reportedly eradicates the virus in 50 % HCV positive patients. However, a number of side effects are associated with the therapy, which may ultimately lead to dose reduction or even discontinuation of therapy on the part of patient or the physician (Alan Francisus *et al.*, 2008). Severe weight loss is a well established side effect associated with interferon therapy and majority of the patients on interferon therapy reportedly suffers from mild to moderate weight loss.

In HCV patients, weight loss and tissue wasting are common, and particularly are highly prevalent in the advance stages of the disease. The researchers have reported a number of causes for interferon therapy-associated weight loss, which primarily include malnutrition, anorexia, infection, and perhaps an HCV-induced hypermetabolic state.

Loss in weight is considered a strong indicator of poor health and hence a poor prognosis outcome. It is, however, well-established that weight loss is closely and positively related with mortality but not if the individuals

have always been lean (Rumpel *et al.*, 1993; cited by Han *et al.*, 2011). Individuals who have been always lean are reportedly to be healthier than those who have the same body weight but who have recently experienced loss in body weight due to conditions that are known to cause weight loss unintentionally. These conditions include but not limited to all types of cancers and a number of chronic heart and lung disease (Seidell and Visscher, 2000).

It is a common experience that such unintentional weight loss presents problems when interpreting body weight in clinical and/or research settings. In addition, intentional weight loss through changes and modification in life style or by medical and pharmaceutical intervention results in a wide range of clinical benefits as well as improvement in quality of life. On the contrary, unintentional weight loss is experienced mostly because of illness and usually is not very well-controlled in the sense that it usually undesirably involves loss of lean body mass, which, no doubt, triggers a poor prognosis, even if there is subsequent weight regain which very often involves accumulation of fat mass and/or edema (Seidell and Visscher, 2000; cited by Han *et al.*, 2011).

There are many factors contributing to weight loss in HCV patients on interferon therapy. These include but not limited to taste changes, low or even diminished appetite,

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nausea, vomiting, depression, stigma, and overactive thyroid etc. Fatigue, cephalgia, weight loss, flu-like syndromes, and anorexia have often been reported by HCV patients during the interferon- α (IFN- α) and/or ribavirin treatment (Mans *et al.*, 2001).

The changes in body weight and body composition are often so fast in onset and much severe in nature that either the patient or the physician is forced to reduce the dose or even discontinue the therapy. A comprehensive understanding of the degree of these changes and the underlying mechanism is, therefore, important from both treatment and prognosis view point. In this review, we present the scope of these changes both as they may affect body weight as a whole as well as other compartments of body composition, most importantly the lean body mass and fat tissues, both of which are relatively more important in the physical and physiological contexts of human body. Also, a critical discussion on the biological mechanism involved in these changes is also presented in order to better understand the disease in a broader scenario instead of as a single entity.

Interferon and ribavirin-an overview

Interferon and ribavirin are considered the gold standards for the treatment of HCV infection (Ascione 2010, Rumi 2010; McHutchison, 2009). Even before when HCV has not been identified as an infectious disease, interferon- α (IFN- α) was successfully used to normalize the so-called transaminases, which consequently led to dramatic improvement in the liver histology in a number of HCV patients. The development of pegylated interferon- α (PEG-IFN- α) improved the pharmacokinetics of IFN (Haagsma 2010). Out of the three common types, IFN- α is considered the most effective. Pegylated interferon is a therapeutically active and clinically safe form of interferon. In practice, polyethylene glycol (PEG), a very well-known chemical, is attached to interferon such that it renders interferon to be more acceptable to the very selective HCV infected biological system of the body. Consequently contrary to interferon alone, PEG-IFN has the ability to remain in the body relatively for longer time but more importantly, it functions more efficiently and yields higher sustained response rate against HCV. Ribavirin and IFN are often used in combination in two distinct forms: either 1) recombinant interferon α -2a or 2) α -2b. Similarly, pegylated interferon (PEG-IFN) is also useable in two distinct forms i.e. pegylated interferon α -2a or 2b) pegylated interferon α -2b. A few years ago, IFN and ribavirin were considered as the 'gold standard' of care for HCV treatment, but combination therapy of PEG-IFN and/or ribavirin is speculated to be the new standard for its safety, less toxicity, fewer side-effects and prolonged sustainability and stability in the body.

Importance of Body Composition and Body Weight

Changes in body composition are considered to be the

most significant in terms of health outcomes and well-being (Song *et al.*, 2004). For example, often a simple measure such as body weight could be a warning sign of more complex problems (Davison *et al.*, 2002) and probably signifies the loss of lean body mass (Alley *et al.*, 2008).

A normal distribution of tissues (fat and lean) and body fluid in the body is associated with overall well-being of the individuals because it also regulates acid-base homeostasis of the body besides many other functions. In healthy individuals, body fluid is distributed equally in the intracellular and extracellular compartments. In healthy individuals, a balance between extra and intracellular water is of vital importance.

Changes in body weight in patient on interferon therapy

HCV patients on PEG-IFN and/or ribavirin therapy experience sudden weight loss which is often severe in terms of total body weight and ranges from 12-29% (Manns *et al.*, 2001; Fried *et al.*, 2002), affecting up to as many as 90% of the patients (Hamer *et al.*, 2008), with probable recovery after treatment (Conjeevaran *et al.*, 2011). Worrisome is the fact that a substantially greater majority of HCV patients on PEG-IFN and/or ribavirin have been reported to suffer from weight loss. There have been reports that as much as 13-20% of patients on PEG-IFN- α -2a and in about 11-29% of patients on PEG-IFN- α -2b suffer from clinically substantial weight loss (Fried, 2002; Scheing Corporation, 2001; Anonymous, 2001; Manns *et al.*, 2001; Fried *et al.*, 2002). Some other investigators have reported even higher number of patients, who suffered from clinically significant weight loss. For example, Hamer *et al.* (2008) reported that 93% of patients had drastic weight loss and substantially decreased energy intake during therapy with PEG-IFN- α -2a and ribavirin. Similarly, in a study by Seyam *et al.* (2005) it was observed that HCV patients on PEG-INF- α -2b lost weight differently during the study period, with majority of the patients (94.7%) lost weight at week 24 (completion of the treatment), while 91.2% of HCV patients lost weight at week 4 and 93.7% at week 12. It is clear from these observations that weight loss is a phenomenon universally common in HCV patients on therapy and that the difference in weight loss prevalence may be due to differences in sample size, socio-geographical and genetic background.

It is, however, worth mentioning here that there are also differences in weight loss in HCV patients, responders, non-responders, and those with relapses. As an example, Conjeevaram *et al.*, (2011) reported significant decrease in body mass index (BMI) as well as in the values of homeostasis model assessment (HOMA) among HCV patients who showed a sustained virologic response (SVR) or responders, non-responder, and those with relapse. Suwantararat *et al.*, (2010) noted the same findings and found that HCV patients with SVR lost weight

significantly as compared to those without SVR. Weight loss in HCV patients with SVR continued during the therapy period, but as soon as the therapy was stopped these patients started to regain weight. This decline in the nutritional status in terms of weight loss may be related to the effect of the side effects of the treatment including nausea, appetite loss, and fatigue. From the above observations, it can be inferred that weight loss in HCV patients during the treatment with PEG-IFN and/or ribavirin is not only a most frequent symptom of adverse effects of the drug but is also an ongoing concern for clinicians and experts who monitor these patients during the therapy (Hamer *et al.*, 2008; Conjeevaram *et al.*, 2011; Gaglio *et al.*, 2011, Khan, S. *et al.*, 2012).

Changes in Body Fat

Body weight is a mix of body fat (fat tissues) and non-fat tissues (lean body mass including mainly muscles, bones, body water etc). Loss in weight means proportionate losses in these components, particularly body fat and lean body mass. This is generally known as segmented loss in body weight.

Weight loss more than 10% of the initial body weight is a warning signal and has been reportedly one of the major causes of weakness in HCV patients. Although loss in muscle mass may be attributed mainly to a persistent inflammatory myopathy, there are reports that only a few patients (3 out of 30: 10%) with HCV infections suffered with muscle wasting who had a specific inflammatory myopathy (Miro *et al.*, 1997). Quite in contrast, fat mass is lost disproportionately in the early stages of wasting; muscle loss predominates in the later stages (Grinspoon *et al.*, 1997).

Body fat mass and hepatic steatosis have been recognized as cofactors for both the presence (Adinolfi *et al.*, 2001; Ortiz *et al.*, 2002; Hourigan *et al.*, 1999) and progression (Adinolfi *et al.*, 2001) of fibrosis in HCV along with male gender, age, and duration of infection (Poynard *et al.*, 2001). Some investigators have focused on changes in body compartments instead of weight loss as a whole. The second issue is based on the notion of fat distribution being more important than the total body fat mass. Visceral fat has been shown to be a predictor of hepatic steatosis in HCV patients and obese individuals (McCullough *et al.*, 1999). Therefore, waist circumferences (not likely to be available in retrospective study) would have been of interest to compare with BMI. It is also noteworthy to consider the possible decrease of inflammation characterized by a decrease in alanine amino-transferase (Irmisch *et al.*, 2011) during treatment that may reflect the decrease in circulating inflammatory cytokines (Cacciarelli *et al.*, 1996), which in turn could contribute to decreased total body fat.

The bottom line of the preceding sections is that loss in

weight and body fat can be used as surrogate markers for the efficacy of IFN therapy. Also, if monitored closely, these values can serve the purpose to evaluate the prognosis of the diseases. Selivestrova *et al.*, (2011) conducted a study to assess prognostic value of body mass index (BMI), percent of body fat (%BF) and waist-to-hip ratio (WHR) on to efficacy of therapy of chronic hepatitis C with PEG IFN- α -2a plus ribavirin. The results showed no difference in mean BMI between patients who achieved and not-achieved SVR. However, they had lower %BF and WHR. The authors concluded that %BF and WHR demonstrate better prognostic value for pegylated interferon ribavirin combination therapy for HCV infection. Similarly, Chua *et al.*, (2011) investigated the relationship between weight loss and sustained virologic response in 194 patients. The authors concluded a relationship between weight loss and SVR and recommended weight loss as a surrogate indicator for IFN/ribavirin efficacy.

Mechanism underlying weight loss due to IFN treatment

The mechanism of weight loss during IFN treatment is not very well-established. Some contributory factors to weight loss extensively reported may include inadequate food intake as a result of drug suppressive appetite effects, cytokine imbalance and dipocytes apoptosis (Seyam *et al.*, 2005; Birk *et al.*, 2006). In HCV patients, no baseline characteristics (e.g. age, gender, weight, ethnicity or histological stage) have been linked to the risk of weight loss (Seyam *et al.*, 2005). In contrast, in another study by Bani-Sadar *et al.*, (2008), older age, and a higher baseline BMI were independent risk factors for severe weight loss.

There are reports regarding decreased appetite with standard IFN therapy (Anonymous, 2001, Manns *et al.*, 2001, Heathcote *et al.*, 2000; Zeuzem *et al.*, 2000), which tempts to postulate that this may be one of the causes of weight loss. However, unfortunately no studies have yet attempted to correlate reported patients' appetite with weight loss and hence it is still to be investigated. A number of mechanisms have been proposed for suppression of appetite and consequently such unintentional weight loss. Induction of tumor necrosis factor (TNF) by IFN might constitute a mechanism for decreased appetite and/or loss of weight. However, some studies have shown that serum TNF levels do not rise during IFN treatment (Cotler *et al.*, 2001; Kallinowski *et al.*, 1998). Indeed, one study showed that IFN may actually suppress TNF exposure via increased production of soluble TNF receptors (Tilg *et al.*, 1995).

A recent study (Matarese *et al.*, 2004) has postulated that cytokines such as IFN could affect the production of hormones such as leptin and insulin, thus affecting glucose metabolism. Some studies have shown that leptin levels fall during IFN therapy (Enjoji *et al.*, 2002; Widjaja

et al., 2001). However, falling serum leptin levels may simply reflect the reduction of body weight during treatment.

The possibility that leptin mediates, to some extent, the weight loss during treatment merits further examination. Higher serum leptin levels have been reported in HCV patients and particular in those with more severe fibrosis or cirrhosis (Bolukbas *et al.*, 2004). Leptin is a member of cytokine family secreted by the adipocytes and known to reduce food intake, mainly related with body fat content and sex, being higher in obese than lean subjects and in females than in males (Ferrua *et al.*, 2002 ; Van Gaal *et al.*, 1999).

Another candidate for further studies would be ghrelin; a previously discovered 28-amino acid peptide (Kojima *et al.*, 1999) has been implicated in the control of food intake and energy homeostasis in both humans (Wren *et al.*, 2001) and rodents (Wren *et al.*, 2001; Tschop *et al.*, 2000; Nkazato *et al.*, 2001). The vast majority of circulating ghrelin is produced in the mammalian gastric mucosa by the enteroendocrine cells/oxynitic glands (Kojima *et al.*, 1999). No study, however, has yet examined ghrelin responses during IFN therapy and further investigation in cross-sectional as well as longitudinal studies recruiting patients of all age groups is needed.

Clinical observations have suggested that ribavirin might potentiate mitochondrial damage in subcutaneous adipose tissue, leading to lipoatrophy and weight loss (Garcia-benayas *et al.*, 2002; Perez-Olmeda *et al.*, 2003; Moreno *et al.*, 2004; Guuyader *et al.*, 2002; Kakuda *et al.*, 2001; Lafeuillade *et al.*, 2001). Mitochondria are found in virtually all eukaryotic cells and function to generate cellular energy in the form of adenosine triphosphate (ATP) by oxidative phosphorylation and are thought to be derived evolutionarily from the fusion of prokaryotic and eukaryotic organisms (Freya and Mannellab, 2000).

No substantially significant data available on lactic acidosis in HCV patients treated with interferon. However, in HIV patients lactic acidosis can occur in patients treated with highly active antiretroviral therapy (HAART), particularly with treatment with the nucleoside reverse transcriptase inhibitors stavudine, didanosine, and zidovudine (Carr *et al.* 2000; Falco *et al.*, 2002), and is associated with fatigue, anorexia, muscle aches, and occasionally severe weight loss.

It is evident from the preceding discussion that the underlying proposed mechanisms involved in weight loss in HCV patients on IFN therapy are not exclusive of each other. Rather, it is equally possible that all these mechanisms may operate simultaneously in such a manner that to reinforce the effects of each other and hence collectively cause a sudden but rapid weight loss as

observed and reported extensively (Mans *et al.*, 2001; Fried *et al.*, 2002; Scheing Corporation, 2001; Anonymous, 2001). Whatever mechanisms at cellular level are involved, a suppression of appetite seems to be universal, which is the major concern for clinicians and health-care providers. As it is a neuro-physiological process and as it is altered in both directions even when there is a minute disturbance at nervous or physiological level, appetite is very likely to change which may consequently cause a reduction in weight loss due to indigenous utilization of stored energy sources (muscles and fat tissues) for the production of energy, a state called negative energy production. The clinicians, therefore, should closely monitor changes in appetite and respond accordingly to correct it with nutritional interventional strategies.

Measures to minimize loss in appetite and weight

As discussed in the above sections, loss in weight and hence in other components of body composition is universal in HCV patients on interferon therapy. It is, therefore, often tempting for the physicians and other health-care providers to advice patients how to minimize weight loss. The following tips are usually of benefits for preventing weight loss (Alan Francisus *et al.*, 2008):

1. Consult with a dietician or nutritionist for information on healthy food choices,
2. Choose foods that are high in calories and protein
Drink clear juices in addition to water for extra calories
3. Add powdered milk to regular milk, milkshakes, soups, eggs, mashed potatoes and puddings
4. Spread peanut butter on bread and fruit Add cooked beans or hard-boiled eggs to soups, and pasta that already contains cheese or meat, if tolerated,
5. Try products designed to promote weight gain, such as nutritional supplements, canned formulas, protein powders, instant breakfast drinks and high-calorie puddings

Conclusions and recommendations

Weight loss and tissue wasting are common in HCV patients on interferon/ribavirin therapy. Involuntary weight loss is associated with disease progression and death, even when access to potent antiretroviral medications is available. Rapid weight loss is usually due to a secondary infection. Weight loss in HCV patients on therapy may be related to the adverse effects of treatment, which may be accounted for loss of appetite, with the consequent decrease in energy intake and disease progression rather than changes in resting energy expenditure. Body fat mass and lean body mass are also affected. The possible mechanisms underlying weight loss or changes in other body composition have been reported and include suppressed appetite due to induction of TNF by IFN, a decrease in serum leptin level, and importantly

mitochondrial damage induced by the therapy. Patients receiving treatment with PEG-IFN and/or ribavirin for chronic hepatitis C must be monitored closely for side effects, importantly those related to weight loss. The clinicians need to have a thorough knowledge of the degree of weight loss and the mechanism involved in changes in weight. Only then, they can provide better treatment to their patients.

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