AGA Clinical Practice Update on Lifestyle Modification Using Diet and Exercise to Achieve Weight Loss in the Management of Nonalcoholic Fatty Liver Disease (NAFLD): Expert Review

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AGA Clinical Practice Update on Lifestyle Modification Using Diet and Exercise to Achieve Weight Loss in the Management of Nonalcoholic Fatty Liver Disease (NAFLD):

Expert Review

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Zobair Younossi: Drafting of the manuscript and critical revision of the manuscript and approved final version

Kathleen Corey: Drafting of the manuscript and critical revision of the manuscript and approved final version

Joseph Lim: Drafting of the manuscript and critical revision of the manuscript and approved final version

All authors approved the final version of this article.

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Abbreviations:

NAFLD- non-alcoholic fatty liver disease
HCC- hepatocellular carcinoma
NASH- nonalcoholic steatohepatitis
BPA- Best Practice Advice
AGA- America Gastroenterological Association
CPUC- Clinical Practice Updates Committee
LM- lifestyle modification
CVD- cardiovascular disease
DM- diabetes mellitus
TBW- total body weight
Kcal- kilocalories
Med- Mediterranean
SFA- saturated fatty acid
SSB- sugar sweetened beverage
IF- intensity factor
MET- metabolic equivalent
IHTG- intrahepatic triglyceride
ACC- American College of Cardiology
AHA- American Heart Association
ABSTRACT

Nonalcoholic fatty liver disease. (NAFLD) is a leading etiology for chronic liver disease with global public health impact, affecting over 25% of the global population. NAFLD is associated with significant morbidity and mortality from cirrhosis, hepatocellular carcinoma (HCC), solid organ malignancies, diabetes mellitus, cardiovascular disease, and obstructive sleep apnea, resulting in significant healthcare resource utilization and decreased health-related quality of life. NAFLD cirrhosis is a leading indication for liver transplantation in the United States. Lifestyle modification to achieve weight loss remains a first line intervention in patients with NAFLD. Herein we summarize evidence-based interventions for lifestyle modification in the treatment of NAFLD and provide Best Practice Advice (BPA) statements to address key issues in clinical management.
# BEST PRACTICE ADVICE STATEMENTS

<table>
<thead>
<tr>
<th>Best Practice Advice (BPA) Statements</th>
<th><strong>BPA 1:</strong> Lifestyle modification using diet and exercise to achieve weight loss is beneficial for all patients with NAFLD.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BPA 2:</strong> Among patients with NASH, weight loss of ≥5% of total body weight can decrease hepatic steatosis, weight loss of ≥7% can lead to NASH resolution, and weight loss of ≥10% can result in fibrosis regression or stability.</td>
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<tr>
<td><strong>BPA 3:</strong> Clinically significant weight loss generally requires a hypocaloric diet targeting 1200-1500 kcal/day or a reduction of 500-1000 kcal/day from baseline.</td>
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<tr>
<td><strong>BPA 4:</strong> Adults with NAFLD should follow the Mediterranean diet, minimize saturated fatty acid (SFA) intake specifically red and processed meat as well as limit or eliminate consumption of commercially produced fructose.</td>
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<tr>
<td><strong>BPA 5:</strong> A hypocaloric diet should be implemented for patients with lean NAFLD (BMI 26 kg/m² non-Asian or BMI 24 kg/m² Asian) with a lower target weight loss threshold of 3-5% as they experience similar histologic benefits for steatosis and NASH as patients with overweight or obese NAFLD.</td>
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<tr>
<td><strong>BPA 6:</strong> The effect of other specific hypocaloric diets such as low carbohydrate/high protein diets, meal replacement protocols, intermittent fasting, and vitamin supplementation on histologic NAFLD endpoints have been inadequately studied to support routine use in NAFLD-specific treatment.</td>
<td></td>
</tr>
<tr>
<td><strong>BPA 7:</strong> Regular physical activity should be considered for patients with NAFLD</td>
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</tr>
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with a target of 150-300 minutes of moderate intensity or 75-150 minutes of vigorous intensity aerobic exercise per week. Resistance training exercise may be complementary to aerobic exercise and may have independent effects on NAFLD. Exercise’s impact on NAFLD can enhance the positive effect of hypocaloric diet.

**BPA 8.** Patients with NAFLD should be evaluated for co-existing metabolic conditions such as obesity, diabetes mellitus, hypertension, dyslipidemia, and cardiovascular disease. These co-morbidities should be aggressively managed.

**BPA 9.** Alcohol consumption should be restricted or eliminated from the diets of adults with NAFLD.

**BPA 10.** Sarcopenia is commonly observed in patients with NASH cirrhosis. This group may require specialized dietary and activity management.
INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), a metabolically derangement-based liver disease, is a leading cause of chronic liver disease with global public health impact, affecting over 25% of the global population. This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the CPUC and external peer review through standard procedures of Gastroenterology. Among those with NAFLD, it is estimated that one in four may have non-alcoholic steatohepatitis (NASH). NASH is associated with significant morbidity and mortality due to complications from cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). In the context of the rising incidence and prevalence of NAFLD in tandem with obesity and metabolic syndrome, NAFLD-associated cirrhosis and HCC is expected to emerge as the leading indication for liver transplantation within the next decade. In addition, patients with NAFLD are also at higher risk of developing non-hepatic solid cancers. NAFLD is also related to increased morality as a result of cardiovascular disease, diabetes mellitus, and lung disease to include obstructive sleep apnea. Finally, NAFLD is not restricted to patients with obesity as recent studies have confirmed that the prevalence of normal weight NAFLD in the general population can range from 4% to 10%. However, within the NAFLD population up to 40% can be considered to be of normal weight depending on the number of metabolic derangements present. Normal weight NAFLD can carry a high morbidity and mortality burden.

Lifestyle modification including significant weight loss through hypocaloric diet and exercise is considered as a first-line intervention for the treatment of NAFLD as weight loss is associated with a reduction in liver fat which provides a potential for reversal of disease progression. As
such, the American Association of Gastroenterology provided guidance on how to manage
obesity care for safe and effective weight management. The guidance centers on four guiding
principles (assessment, intensive weight loss intervention, weight stabilization and re-
intensification if needed, and prevention of weight regain) obtained through a reduced calorie
diet, physical activity, medications, bariatric endoscopy, and surgery to achieve weight loss.\textsuperscript{13}
However, medications, bariatric endoscopy, and surgery to achieve weight loss, are largely
focused on subsets of patients with severe obesity, co-existing diabetes mellitus, and/or biopsy-
proven NASH with, at a minimum, stage 2 fibrosis. \textit{Therefore, lifestyle modification using diet
and exercise to achieve weight loss remains the cornerstone for the management of NAFLD.}\textsuperscript{13}

This review then is designed to provide this guidance on the key clinical issues need to achieve
weight loss through lifestyle modification focused on diet and exercise for patients with NAFLD.
We have developed Best Practice Advice (BPA) statements to address ten key clinical issues.
This review has undergone internal peer review by the CPUC and external peer review through
standard procedures of the journal. However, it is important to note that these guidance
statements require a team approach to improve adherence such that the use of personnel educated
in diet and in exercise should be incorporated so that each patient’s diet and exercise plan can be
individualized to be culturally sensitive, socially appropriate, obtainable, and measurable.\textsuperscript{14}

\textbf{BPA 1: \textit{Lifestyle modification using diet and exercise to achieve weight loss is beneficial for
all patients with NAFLD.}}

Lifestyle modification (LM) centered on diet and physical activity (as described in detail below)
to achieve weight loss as well as the avoidance of alcohol are the foundations of treatment for all
patients with NAFLD, regardless of histologic type. NAFLD is a risk factor for diabetes mellitus (DM), cardiovascular disease (CVD), and cancer both liver and non-liver related. The reduction of body weight results in decreased liver fat and improved glucose control/insulin sensitivity reducing the risks for DM, CVD, as well as decreasing the risks of progressive liver disease (discussed below). Research is needed to determine the impact of weight loss, NAFLD and the development of uterus, stomach, pancreas, and colon cancers.

BPA 2: Among patients with NASH, weight loss of $\geq 5\%$ total body weight (TBW) can decrease hepatic steatosis, weight loss of $\geq 7\%$ can lead to NASH resolution, and weight loss of $\geq 10\%$ can result in fibrosis regression/stability.

Weight loss improves multiple facets of NAFLD histology. A randomized controlled trial compared 48 weeks of an intensive lifestyle intervention (ILI) including caloric reduction and physical activity to standard structured education on weight loss and NASH histology. While the control had no significant change in weight, the ILI group lost on average 9.3% TBW. Participants with $\geq 7\%$ TBW loss had significant improvement in steatosis, lobular inflammation, hepatocyte ballooning and NAFLD activity score (NAS) although no change in fibrosis was seen. A second prospective cohort examined the impact of higher degrees of weight loss on histology and found that after 1 year of ILI among those who achieved a 5-6.99% TBW loss, 65% had improvement in steatosis. Among those who achieved a 7-8.99% TBW loss, 64% had NASH resolution and among those with $\geq 10\%$ TBW loss 45% had fibrosis regression of at least one stage while the remaining 55% had fibrosis stabilization. These findings demonstrate that weight loss can significantly impact all aspects of NAFLD histology including fibrosis but a goal of 10% TBW loss should be considered for patients with overweight or obese NAFLD. In addition to this pivotal trial, several systematic reviews and meta analyses have
reported similar findings on diet and exercise highlighting that the more intensive the weight loss
intervention the more weight loss occurs which can lead to improved NAFLD related liver
biomarkers.\textsuperscript{18-20}

\textbf{BPA3: Clinically significant weight loss generally requires a hypocaloric diet targeting
1200-1500 kcal/day or a reduction of 500-1000 kcal/day from baseline.}

Hypocaloric diets are an important component in the treatment of NAFLD. Hypocaloric diets are
characterized by a decrease in daily caloric intake by 500-1000 kilocalories (kcal) per day or to a
target of 1200 kcal/daily for women and 1400-1500 kcal/daily for men. Hypocaloric diets are
associated with weight loss as well as improvements in insulin resistance, decrease in liver
enzymes and intrahepatic fat.\textsuperscript{5,6} The improvements in intrahepatic fat following a hypocaloric
diet may persist even with weight regain two years after weight loss.\textsuperscript{8} However, data are
lacking as to the long term effect of very low hypocaloric diets (\textasciitilde 800 Kcal/day) in those with
NAFLD, though one very small study reported reversal of NAFLD by day 28 on a 800 kcal/day
among women with obesity.\textsuperscript{21}

\textbf{BPA 4: Adults with NAFLD should follow the Mediterranean diet or a diet of similar
design, minimize saturated fatty acid (SFA) intake specifically red and processed meat and
commercially produced fructose consumption}

Several diets may be appropriate for weight loss in those with NAFLD \textsuperscript{22-24}, however, the
Mediterranean diet (Med diet) has been the most studied for those with NAFLD/NASH and is
thought to reduce the risk of and progression of NAFLD through the nutraceutical effect of
bioactive compounds and phytochemicals with their antioxidant and anti-inflammatory capacity
associated with the ingestion of certain fibers, monounsaturated and omega-3 fatty acids and phytosterols found in the Med diet. 25-26

The Med Diet is characterized by daily consumption of fresh vegetables, fruit, legumes, minimally processed whole grains, and fish along with omega-3-fatty acids such as olive oil, nuts and seeds as the primary fat sources with minimal to low consumption of diary, red and processed meat. 27 The Med diet is beneficial in the prevention and treatment of multiple metabolic conditions including cardiovascular disease and diabetes mellitus and is associated with a decrease in overall mortality. 28 Among adults with NAFLD, the Med diet, even in the absence of weight loss, leads to a reduction in hepatic steatosis with an increase in insulin sensitivity compared to a low, high carbohydrate diet. 28 A recent study from the Framingham Heart Study found that for every standard deviation increase in the Mediterranean Diet Score (a measure of Med diet consumption) the odds for incident fatty liver decreased by 26%. An increased Mediterranean Diet Score was also found to be associated with reduced liver fat accumulation and severity. 29

Foods rich in saturated fatty acids (SFA) such as meat are associated with both cardiovascular disease and diabetes mellitus. 30 Total meat consumption (≥1.1 portions/day or ≥7.7 portions per week), red meat (≥0.33 portions per day or ≥2.3 portions per week), and processed meat (≥0.10 portions per day or ≥0.7 portions per week) are associated with NAFLD and should be limited. 31

While the impact of eliminating meat from the diet on NAFLD has not yet been evaluated, limiting the overall meat intake and avoidance of the processed meats in patients with NAFLD should be considered.
Increased consumption of fructose, predominantly high-fructose corn syrup in sugar-sweetened beverages (SSB), is associated with post-prandial hypertriglyceridemia and visceral adiposity contributing to insulin resistance and NAFLD.\textsuperscript{32,33} Among adults with NAFLD, fructose consumption, quantified by consumption of SSB, is associated with higher fibrosis stages. Furthermore, among older adults, fructose consumption is associated with increased hepatic inflammation and hepatocellular ballooning.\textsuperscript{33} However, fructose contained in fruits is not associated with NAFLD so fruit consumption should not be restricted.\textsuperscript{34}

**BPA 5: A hypocaloric diet should be considered as treatment for patients with normal weight NAFLD (BMI ≤ 25 kg/m\textsuperscript{2} non-Asian or BMI ≤ 23 kg/m\textsuperscript{2} Asian) with a lower target weight loss threshold of 3-5% as they experience similar histologic benefits for steatosis and NASH as patients with overweight or obese NAFLD.**

Patients considered to be of normal weight have NAFLD and the severity depends on the metabolic derangements present. However, there is little published on the management of normal weight NAFLD although the few published have suggested that those with normal weight NAFLD can significantly benefit from ILI and weight loss through improvement of hepatic fat, decreased waist circumference, and decreased low-density lipoprotein (LDL) levels. Similar to patients with obesity and NAFLD, a reduction of body weight and remission of NAFLD is dose dependent for those with normal weight NAFLD. In adults with normal weight NAFLD, a 3-5% TBW loss can also result in NAFLD resolution in 50% and a 7–10% TBW loss results in resolution of NAFLD in 70\%.\textsuperscript{35,36} Liver stiffness assessed by transient elastography also improved in those with normal weight NAFLD who participated in the lifestyle intervention when compared to those in the control arm.\textsuperscript{35} The durability of weight loss and the impact of weight regain in normal weight NAFLD is not known.
BPA 6: The effect of specific hypocaloric diets such as low carbohydrate/high protein diets, meal replacement protocols, intermittent fasting, and vitamin supplementation on histologic NAFLD/NASH endpoints have been inadequately studied; however, there are potential benefits of certain hypocaloric diets to treat patients with NAFLD which require an individual approach before prescribing.

Studies of meal replacement diets for the treatment of NAFLD have been limited by small size and have failed to demonstrate a benefit in NAFLD. Intermittent fasting (IF), also known as time restricted eating, limits the hours or days that calories are consumed and should be individualized. A study of alternate day fasting in adults with NAFLD lead to weight loss and improvement in lipid parameters but no change in liver stiffness by transient elastography. A second study of IF was associated with a reduction in the fatty liver index in adults with and without diabetes mellitus. Both studies are limited by lack of radiographic or histologic endpoints and further studies are needed before IF can be routinely considered for the treatment of NAFLD.

Low carbohydrate, high protein diets have been studied for weight loss in obesity but limited data exists in NAFLD. A single study found that a low carbohydrate, high protein diet resulted in weight loss and improvement in liver enzymes but no data on radiographic or histologic improvement was ascertained. A second study evaluated the impact of a low carbohydrate diet and a high carbohydrate diet on intrahepatic triglyceride (IHTG) content and found that at 48 hours those on the low carbohydrate diet had significant greater decreases in IHTG but after 11 weeks, there was no difference by diet on IHTG content. Thus, a high protein, low carbohydrate diet cannot yet be considered as the preferred diet for the treatment of
NAFLD. Patients should be counseled to follow a Mediterranean diet as above and modulate the carbohydrate and protein content that best suits them.

Vitamin E, based on the results of the PIVENS trial, is currently recommended as a treatment for biopsy-proven NASH in adults without diabetes. However, while vitamin E improved several aspects of NASH histology, it had no benefit on fibrosis which is the only variable associated with mortality. Furthermore, Vitamin E may be associated with increased risks of prostate cancer and all-cause mortality, limiting its use. Similarly, vitamin C, in high doses may impact several aspects of NASH histology but results have been conflicting regarding the impact of vitamin C on fibrosis and further evaluation is needed before it can be considered for routine use.\textsuperscript{40}

BPA 7: Regular physical activity should be considered to patients with NAFLD with a target of 150-300 minutes of moderate intensity or 75-150 minutes of vigorous intensity aerobic exercise per week. Resistance training may be complementary to aerobic exercise but not a replacement.

Exercise’s impact on NAFLD can enhance the positive effect of hypocaloric diet. Physical activity, independent of weight loss, can improve NAFLD by reducing hepatic fat content, in part by improving the body’s peripheral sensitivity to insulin, decreasing hepatic de novo lipogenesis, decreasing adipocyte lipolysis and reducing free fatty acid delivery to the liver.\textsuperscript{36,41}

Physical activity can be accomplished through aerobic activity such as walking or stationary biking while resistance training is accomplished with load-lifting exercises such as weight training using a weight machine. A systemic review and meta-analysis assessing the impact of exercise on NAFLD found that exercise alone (predominantly aerobic exercise), without dietary intervention, significantly decreased liver fat with a non-significant trend toward improvement in
ALT compared to control groups. Individual studies have varied by aerobic exercise type and duration; however, benefits for steatosis were seen with 90-300 minutes per week. As such, in general 150-300 minutes of moderate intensity exercise (3-6 METS) or 75-150 minutes of vigorous intensity exercise (>6 MET) should be considered for patients. Resistance training has been shown to decrease steatosis with lower intensity than aerobic exercise and may be an option for those with limited aerobic capacity; however, in a most recent population based study, walking greater than three hours a week was associated with decreased cirrhosis related deaths and HCC so encouragement for aerobic activity should be considered. It is important to note that exercise seems to enhance the weight reduction benefit of diet so moderate physical activity in conjunction with the Mediterranean diet may be associated with the most weight loss as well as reduction in visceral adipose tissue and percent intrahepatic fat.

**BPA 8. Patients with NAFLD should be evaluated for co-existing metabolic conditions such as obesity, diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, and obstructive sleep apnea. These co-morbidities should be aggressively managed.**

The presence of co-existing metabolic conditions in those with NAFLD and NASH are quite high. In a recent meta-analysis on the global burden of NAFLD, investigators reported the pooled overall prevalence estimates of obesity, diabetes, hyperlipidemia, hypertriglyceridemia, hypertension and metabolic syndrome among NAFLD and NASH patients (Table 1) so practitioners should have a high index of suspicion when evaluating patients. Obstructive sleep
Apnea (OSA) is also a common comorbidity associated with higher morbidity and mortality so further investigation for OSA may be warranted.\textsuperscript{43} Since these co-morbidities are also associated with the development of CVD, CVD remains one of the major causes of death among those with NAFLD and or NASH and as such, patients with NAFLD and NASH with these co-morbidities should be referred for further evaluation of cardiovascular (CV) health.\textsuperscript{44} Therefore, we suggest that all those with NAFLD and co-existing metabolic conditions such as obesity, diabetes mellitus, hypertension, and hyperlipidemia be risk stratified for CVD and treated as per ACC/AHA guidelines in addition to the weight management strategies as fully described in the AGA POWER program.\textsuperscript{13,45}

**BPA 9. Alcohol consumption should be restricted in the diets of adults with NAFLD.**

Conflicting data exist on the contribution of alcohol consumption in the development and progression of NAFLD. Cross-sectional studies suggested that low to moderate alcohol use is associated with decreased odds of NASH, hepatocyte ballooning, and fibrosis in NAFLD. However, studies have been limited by their cross-sectional nature and inability to establish causality. A recent large prospective study of alcohol and NAFLD has provided important evidence that alcohol use, even at low levels, is associated with increased liver-related outcomes in those with NAFLD. This study, which evaluated 8,345 with NAFLD (fatty liver index >60), found that after a mean follow-up time of 11.1 years, 9-20 grams of daily general alcohol use or 0-9 grams of daily non-wine alcohol use, compared to lifetime abstainers doubled the risk for adverse liver-related outcomes. Only among never smokers was alcohol use (up to 49 grams daily) associated with a decreased risk of cardiovascular events and death.\textsuperscript{46} Therefore, adults
BPA 10. Sarcopenia is commonly observed in patients with NASH cirrhosis. This group may require specialized dietary and activity management.

Sarcopenic obesity (low muscle mass in the presence of obesity) in cirrhosis is associated with poor clinical outcomes including increased mortality. A recent study found that among patients with cirrhosis who were on the waiting list for liver transplantation, 59% had sarcopenia. Investigators found that obesity and age were independently associated with pretransplant sarcopenia while NASH as an etiology of cirrhosis was also an independent predictor of sarcopenic obesity. In fact, those with NASH cirrhosis were six times more likely to have sarcopenic obesity. In this context, it is important to address sarcopenia in patients with NASH.

Over the past decade, there has been substantial research to better understand the underlying mechanisms of sarcopenia in cirrhosis. In this context, it is believed that the inability of the cirrhotic liver to store, synthesize and mobilize carbohydrates causes patients to rapidly transition to a catabolic state in which protein and fat are used as energy sources. This imbalance between protein synthesis and muscle tissue breakdown, increased autophagy and proteasomal activity, and impaired mitochondrial function in cirrhotic patients independently contribute to the development of sarcopenia. To avoid caloric deficits, an individualized dietary plan should be devised to meet required caloric and nutritional requirements. In this context, the minimum protein intake 1.2-1.5 g/kg with branched chain amino acids obtained from protein sources such as chicken, fish, eggs, nuts, lentils and/or soy should be considered. Patients should be encouraged to eat frequent small meals and avoid more than 4 to 6 hours between meals. As
such, a bedtime snack containing protein and at least 50 g of complex carbohydrates should be considered. Given the complexity of the nutritional needs of this group, consultation with a specialized nutritionist is preferred. In additional to dietary changes, moderate intensity exercise may be beneficial, ideally for a duration of 150 minutes per week. In summary, given the high prevalence of sarcopenia in cirrhosis, and its impact on long-term outcome, further research to characterize the mechanisms of sarcopenia and elucidate targets for novel therapy are needed.

**Conclusions**

Lifestyle modifications which include diet and physical activity to achieve weight loss, are the cornerstone of treatment for NAFLD. Additionally, restriction or elimination of alcohol consumption and optimal management of cardiometabolic comorbidities are also highly important. In this expert review, we provide practical advice through 10 BPA’s to help practitioners in their development of a treatment plan for their patients with NAFLD to include treatment of sarcopenia in NASH cirrhosis.
Table 1: Prevalence of Selected Co-Morbidities in Patients with NAFLD and NASH*

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>NAFLD (%)</th>
<th>NASH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>51.3</td>
<td>81.8</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>22.5</td>
<td>43.6</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>69.2</td>
<td>72.1</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>40.7</td>
<td>83.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>39.3</td>
<td>68.0</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>42.5</td>
<td>70.7</td>
</tr>
</tbody>
</table>

References


