Efficacy and Safety of Diflstat® for the Treatment of Secondary Dyslipidemia in Chronic Kidney Disease

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Ethics

Informed consent was obtained from all patients, according to the recommendations of the declaration of Helsinki guiding physicians in biomedical research involving human subjects. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983 and the 41st World Medical Assembly, Hong Kong, September 1989. The work was approved by the ethical panel of our institution.

Abstract: 1104 patients with Secondary Dyslipidemia and CKD (Chronic Kidney Disease) (females: 387; males: 717; aged: 70 ± 11 years) were given Diflstat® with diet to evaluate efficacy and safety. The study lasted two years. Patients were assigned to three groups (A, B, C) based upon basal renal function. Group A consisted of 180 patients with GFR (glomerular filtration rate) of 67 ± 16 mL/min/m². TC (Total-Cholesterol) (-31%), LDLC (LDL-Cholesterol) (-42%), TG (triglycerides) (-36.8%) levels, and non-HDLC (non HDL cholesterol) (-41%) and TC/HDLC ratio (-40%) were significantly reduced ($P < 0.001$). GFR (+2.5%) increased significantly. No significant changes were observed in HDLC (+13%). Group B was of 744 patients, 69% (males: 514), 31% (females: 230) (median age: 70 ± 13 years), and moderate stage III CKD (GFR: 38 ± 12 mL/min/1.73m²). After 24 months the change of HDLC (+3.5%) was not significant, while TC (-27%), TG (-32%), LDLC (-33%), non-HDLC (33.4%), TC/HDLC (-30%), and GFR (+2.1%) were statistically significant ($P < 0.001$). Group C consisted of 180 patients, 51.6% (males: 93), 48.3% (females: 87) (median age: 72 ± 11 years), with severe stage IV CKD (GFR: 19 mL/min/1.73m²). HDLC (+13%) was not significant, while TC (-32%), TG (-38%), LDLC (-35%), non-HDLC (-38.5%), TC/HDLC (-40%), and GFR (+2.1%) were statistically significant ($P < 0.001$). An effective but safe lipid-lowering therapy in patients with CKD, may be crucial to prevent cardiovascular events. The treatment with Diflstat® combined with diet is to be started as soon as possible in patients with CKD in order of improving lipid and lipoprotein profile, and reducing the progression of renal damage.

Key words: Secondary dyslipidemia, chronic kidney disease, glomerular filtration rate, albuminuria, cardiovascular risk.

1. Introduction

CKD (Chronic Kidney Disease) is an ever-increasing clinical condition marked by a progressive reduction of kidney function. The primary causes of CKD are an ageing population and kidney complications due to systemic diseases such as arterial hypertension, type II diabetes mellitus, and dyslipidemia. One of the most important risk factors for mortality and morbidity as well as for cardiovascular events and progressive kidney disease is dyslipidemia in a patient with CKD [1]. Of note, it is the risk increase of CVD (cardiovascular disease) at the early stages of CKD [2]. The lipid profile in the majority of patients with CKD is characterized by both quantitative and qualitative changes in circulating lipoproteins [3]. This profile, characterized by a reduction in HDLC (HDL (High Density Lipoprotein)-cholesterol) and a TC (total...
cholesterol) and LDLC (LDL (Low Density Lipoprotein) -cholesterol) levels which can be found reduced, normal or elevated. On the contrary, TG (triglycerides) are often elevated due to a deficit in the catabolism of triglyceride-rich lipoproteins [4, 5]. This phenomenon is caused primarily by a reduced lipolytic activity either by HL (hepatic lipase), or adipose tissue LPL (lipoproteinlipase), or due to factors related to the uremic syndrome (uremic toxins) [6]. In addition, the reduced apo CII/apo CIII ratio may induce an impairment of inhibiting factors (apo CIII) compared with those stimulating (apo CII) lipolysis [7]. Peripheral tissue resistance to insulin and secondary hyperparathyroidism and uremic toxins are the primary causes of lipid pattern change in patients with CKD [8]. A second important pathogenic cause of dyslipidemia during the course of CKD is evidenced by a defective centripetal cholesterol transport mechanism responsible for a reduced LCAT (lecithin-cholesterol acyltransferase) activity [9]. Even in this case, uremic toxins are thought to be responsible [10]. More relevant is surely the reduction of apolipoprotein AI activator of LCAT and major protein of HDL [11]. Patients with CKD exhibit a marked difficulty in removing cholesterol from extrahepatic tissues, vascular primary tissues, esterification and transport from HDL to VLDL (very low density lipoproteins) and LDL [12]. The reduction of HDLC levels in plasma, and consequently the increase of LDL/HDL ratio, is typical in advanced stages of CKD. Patients with CKD exhibit an increase of LDLC particles which are “small and dense” (sd LDL) and of LDL particles which are oxidized, and of IDL (intermediate density lipoprotein) [13]. These “modified” lipoproteins, which are attracted to macrophages, infiltrate the vascular walls and become part of foam cell formation leading to the development of arterial plaque [14]. Patients with CKD exhibit frequently high levels of lipoprotein (a) [Lp(a)] due to a reduced clearance. The highest levels of Lp(a) are found in patients undergoing dialysis treatment [15-17]. MP (Monascus purpureus) is a fungus used in China to produce rice wine. MP induces the fermentation of cellulose, maltose, fructose and glucose. On the other hand, fermentation is due to two microorganisms: MP and a kind of mold. MP changes starch into molecules of sugar, while the second transforms such molecules into alcohol. MP is used in China in the treatment of dyslipidemia [18]. In Western countries, the use is often limited to the pigmentation of foods: meat, fish, cheese, alcoholic drinks and cured meats. The cholesterol-lowering efficacy of MP was evaluated through experimental and clinical trials [19]. By acting through the direct inhibition of 3-hydroxy-3-methylglutaryl coenzymeA reductase, MP could partially have the same effect of statins [20]. In order to enhance the safety by administering the lowest dose without losing its cholesterol-lowering effect, MP was combined with LAAs (Linear Aliphatic Alcohols). LAAs have a synergistic effect with MP, as they downregulate 3-hydroxy-3-methylglutaryl coenzymeA reductase. MP and LAAs showed a lowering effect on cholesterol, but not on TG. N (Niacin) was added because of its well-known triglyceride-lowering effect. If given at high doses, N is also credited to be able at increasing HDLC.

The scope of observation, which lasted 24 months, was to evaluate the efficacy of Dif1stat® [Composition: MP, dry extract, 200 mg (corresponding to 3 mg of mevinolin) + LAAs, 10 mg + N, 27 mg] combined with a hypolipidemic diet on the lipid profile of patients suffering from CKD (II, III, IV stages of CKD according to the Kidney Disease Outcomes Quality Initiative-KDOQI-classification).

Tolerability and safety were evaluated through the eventual appearance of albumin in patients’ urine and usual safety parameters determination.

2. Materials and Methods

2.1 Patients

1104 patients with a median age of 70 ± 11.3 years
were submitted to treatment. 65% \((N = 717)\) were males, while 35% \((N = 387)\) were female. The study lasted for two years. Patients were assigned to three groups (A, B, C) based upon basal renal function (Table 1). Group A consisted of 180 patients with calculated GFR (glomerular filtration rate) of 67 ± 16 mL/min/m² (stage II of CKD according to NKF KDOQI™ (the National Kidney Foundation Kidney Disease Outcomes Quality Initiative), Group B consisted of 744 patients with calculated GFR of 38 ± 12 mL/min/m² (stage III of CKD according to KDQOI classification). Group C consisted of 180 patients with calculated GFR (glomerular filtration rate) of 19 ± 6 mL/min/m² (stage IV of CKD according to KDOQI classification).

2.2 Exclusion Criteria
No patient exhibited hematologic, hepatic, thyroid or neoplastic diseases. Patients with cardiac disease, patients with proteinuria due to nephrotic and nephritic syndromes as well as diabetes, were excluded. None of the patients were given drugs to treat metabolic/lipid disorders, beta-blockers, diuretics, corticosteroids.

2.3 Laboratory
LDLC plasma cholesterol was calculated using the Friedewald formula: LDLC = TC - (HDLC - TG/5) [21]. Non-HDLC cholesterol was calculated using the non-HDLC = TC - HDLC formula. GFR was calculated using CKD-EPI (The Chronic Kidney Disease Epidemiology Collaboration) Creatinine Equation [22].

3. Results of Statistical Analysis
Statistical analysis was performed according to parametric tests, depending on parameters under evaluation. All results are expressed as means ± SD. Within group and between groups differences were tested for statistical significance using Students’ test for paired data. The percent variation \(\Delta\) of mean lipid, lipoprotein levels in plasma, and glomerular filtrate rate was also estimated.

3.1 Group A
Group A consisted of 180 patients, 61.1\% \((N = 110)\) were males, while 38.8\% \((N = 70)\) were female with a median age of 69 ± 10 years and calculated GFR of 67 ± 16 mL/min/m² (Table 1). After 6 months, the variations of TC (-15.6\%) and HDLC (4.3\%) with TC/HDLC (-19\%) and GFR (0.3\%) were not statistically significant. However, variations of TG (-21\%), of LDLC (-20\%), and of non-HDLC (-20\%) were statistically significant for \(P < 0.001\) after six months of treatment. After 12 months, reductions of TC (-22\%), TG (-30\%), LDLC (-28\%), non-HDLC (-29\%) and of TC/HDLC (-28\%) resulted statistically significant for \(P < 0.001\), while no statistically significant increase of GFR (+1.2\%) and HDLC (+8.6\%) was noted. The same decrease was also noted for TC (-26\%), TG (-35\%), LDLC (-34\%), non-HDLC (-34\%), TC/HDLC (-33\%) and GFR (2.23\%) for \(P < 0.001\). The variation of HDLC (10.8\%) did not result statistically significant after 18 months. The decrease of TC (-31\%) TG (-36.8\%), LDLC (-42\%), non-HDLC (-41\%), and of TC/HDLC (-40\%) resulted statistically significant for \(P < 0.001\). GFR (+2.5\%) was statistically significant, too (Figs. 1, 4). No significant variations were noted in HDLC (+13\%) after 24 months of treatment (Table 2).

3.2 Group B
Group B consisted of 744 patients, 69\% \((N = 514)\)
were males, while 31% (N = 230) were female with a median age of 70 ± 13 years, and moderate stage III CKD (GFR 38 ± 12 mL/min/1.73 m²) (Table 1). The variations of TC (-7.4%), HDLC (0.95%), TG (-12%), LDLC (-8.4%), TC/HDL ( -8.2%), non-HDLC (-8.9%), and of GFR (0.26%) were not statistically significant after 6 months of treatment. After 12 months of treatment, changes of TG (-20%) and GFR (1.31%) were statistically significant for $P < 0.001$, while variations in TC (-14%), HDLC (2.38%), LDLC (-18%), non-HDLC (-17%), and TC/HDL (-16%) were not significant. After 18

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**Fig. 1** Group A: Stage II of CKD according to KDOQI classification. 180 patients with GFR (glomerular filtration rate) calculated at 67 ± 16 mL/min/m². The percent variation (Δ%) in plasma of non-HDLC (non-high density lipoprotein cholesterol) and TC/HDL in patients with secondary dyslipidemia, after 6 (T6), 12 (T12), 18 (T18) and 24 (T24) months treatment with Diflstat®, *$P \leq 0.001$.

**Fig. 2** Group B: Stage III of CKD according to KDOQI classification. 744 patients with GFR (glomerular filtration rate) calculated at 38 ± 12 mL/min/m². The percent variation (Δ%) of plasma non-HDLC (non-high density lipoprotein cholesterol) and TC/HDL in patients with secondary dyslipidemia, after 6 (T6), 12 (T12), 18 (T18) and 24 (T24) months treatment with Diflstat®, *$P \leq 0.001$. 

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Note: The diagrams are placeholders and should be replaced with actual visual data from the document.
Fig. 3  Group C: Stage IV of CKD according to KDOQI classification. 180 patients with glomerular filtration rate (GFR) calculated at 19 ± 6 mL/min/m². The percent variation (Δ%) of plasma non-high density lipoprotein cholesterol (non-HDLC) and TC/HDLC in patients with secondary dyslipidemia, at baseline (T0), after 6 (T6), 12 (T12), 18 (T8) and 24 (T24) months treatment with Diflstat®. * P ≤ 0.001.

Fig. 4  The percent variation (Δ%) of plasma TG (triglycerides), LDLC (low-density lipoprotein-cholesterol), in patients with secondary dyslipidemia, after 24 months treatment with Diflstat®. * P ≤ 0.001.

months of treatment, variations of GFR (+1.57%), TC/HDLC (-21.4%), non-HDLC (-23.2%) LDLC (-22%), and TG (-28%) were statistically significant for P < 0.001, while TC (-19%) and HDLC (+2.9%) were not significant. After 24 months the change of HDLC (+3.5%) was not significant, while TC (27%), TG (-32%), LDLC (-33%), non-HDLC (33.4%), TC/HDLC (-30%), and GFR (+2.1%) resulted statistically significant for P < 0.001 (Table 3 and Figs. 2, 4).

3.3 Group C

Group C consisted of 180 patients, 51.6% (N = 93) were males, while 48.3% (N = 87) were female with a
Table 2 Group A: Stage II of CKD according to KDOQI classification.

<table>
<thead>
<tr>
<th>Months</th>
<th>T0</th>
<th>T6</th>
<th>Δ%</th>
<th>P</th>
<th>T12</th>
<th>Δ%</th>
<th>P</th>
<th>T18</th>
<th>Δ%</th>
<th>P</th>
<th>T24</th>
<th>Δ%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>251.4 ± 41</td>
<td>212 ± 23</td>
<td>-15.6</td>
<td>n.s</td>
<td>196.2 ± 39</td>
<td>-22</td>
<td>0.001</td>
<td>186 ± 62</td>
<td>-26</td>
<td>0.001</td>
<td>172 ± 83</td>
<td>-31</td>
<td>0.001</td>
</tr>
<tr>
<td>HDLC</td>
<td>46 ± 12</td>
<td>48 ± 16</td>
<td>4.3</td>
<td>n.s</td>
<td>50 ± 21</td>
<td>8.6</td>
<td>n.s</td>
<td>51 ± 18</td>
<td>10.8</td>
<td>n.s</td>
<td>52 ± 35</td>
<td>13</td>
<td>n.s</td>
</tr>
<tr>
<td>TG</td>
<td>152 ± 46</td>
<td>120 ± 75</td>
<td>-21</td>
<td>0.001</td>
<td>106 ± 45</td>
<td>-30</td>
<td>0.001</td>
<td>98 ± 61</td>
<td>-35</td>
<td>0.001</td>
<td>96 ± 40</td>
<td>-36.8</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>175 ± 38</td>
<td>140 ± 47</td>
<td>-20</td>
<td>0.001</td>
<td>125 ± 52</td>
<td>-28</td>
<td>0.001</td>
<td>115 ± 62</td>
<td>-34</td>
<td>0.001</td>
<td>101 ± 51</td>
<td>-42</td>
<td>0.001</td>
</tr>
<tr>
<td>non-HDL-C</td>
<td>205 ± 23</td>
<td>164 ± 41</td>
<td>-20</td>
<td>0.001</td>
<td>146 ± 19</td>
<td>-29</td>
<td>0.001</td>
<td>135 ± 26</td>
<td>-34</td>
<td>0.001</td>
<td>120 ± 31</td>
<td>-41</td>
<td>0.001</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>5.4</td>
<td>4.4</td>
<td>-19</td>
<td>n.s</td>
<td>3.9</td>
<td>-28</td>
<td>0.001</td>
<td>3.6</td>
<td>-33</td>
<td>0.001</td>
<td>3.3</td>
<td>-40</td>
<td>0.001</td>
</tr>
<tr>
<td>GFR</td>
<td>67 ± 16</td>
<td>67.2 ± 14</td>
<td>0.3</td>
<td>n.s</td>
<td>68 ± 17</td>
<td>1.2</td>
<td>n.s</td>
<td>68.5 ± 16</td>
<td>2.23</td>
<td>0.001</td>
<td>68.7 ± 12</td>
<td>2.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Albuminuria: negative

180 patients with GFR (glomerular filtration rate) calculated at 67 ± 16 mL/min/m².

The percent variation (Δ%) and mean changes (mg/dL ± SD) in plasma lipid and lipoprotein profile and GFR, at baseline (T0), after 6 (T6), 12 (T12), 18 (T18) and 24 (T24) months treatment with Dif1stat®.

HDLC: high density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; TC: total cholesterol; non-HDL-C: non high density lipoprotein-cholesterol; TG: triglycerides; n.s = not significant; n/a = not applicable; P value ≤ 0.001.

Table 3 Group B: Stage III of CKD according to KDOQI classification.

<table>
<thead>
<tr>
<th>Months</th>
<th>T0</th>
<th>T6</th>
<th>Δ%</th>
<th>P</th>
<th>T12</th>
<th>Δ%</th>
<th>P</th>
<th>T18</th>
<th>Δ%</th>
<th>P</th>
<th>T24</th>
<th>Δ%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>269.8 ± 65</td>
<td>249.8 ± 73</td>
<td>-7.4</td>
<td>n.s</td>
<td>232 ± 59</td>
<td>-14</td>
<td>n.s</td>
<td>218 ± 46</td>
<td>-19</td>
<td>n.s</td>
<td>195.2 ± 81</td>
<td>-27</td>
<td>0.001</td>
</tr>
<tr>
<td>HDLC</td>
<td>42 ± 19</td>
<td>42.4 ± 22</td>
<td>0.95</td>
<td>n.s</td>
<td>43 ± 24</td>
<td>2.38</td>
<td>n.s</td>
<td>43.2 ± 31</td>
<td>2.9</td>
<td>n.s</td>
<td>43.5 ± 47</td>
<td>3.5</td>
<td>n.s</td>
</tr>
<tr>
<td>TG</td>
<td>184 ± 99</td>
<td>162 ± 152</td>
<td>-12</td>
<td>n.s</td>
<td>147 ± 90</td>
<td>-20</td>
<td>0.001</td>
<td>131 ± 103</td>
<td>-28</td>
<td>0.001</td>
<td>125 ± 94</td>
<td>-32</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>190 ± 48</td>
<td>174 ± 94</td>
<td>-8.4</td>
<td>n.s</td>
<td>156 ± 56</td>
<td>-18</td>
<td>n.s</td>
<td>148 ± 71</td>
<td>-22</td>
<td>0.001</td>
<td>126 ± 34</td>
<td>-33</td>
<td>0.001</td>
</tr>
<tr>
<td>non-HDL-C</td>
<td>227.8 ± 52</td>
<td>207.4 ± 44</td>
<td>-8.9</td>
<td>n.s</td>
<td>189 ± 39</td>
<td>-17</td>
<td>n.s</td>
<td>174.8 ± 63</td>
<td>-23.2</td>
<td>0.001</td>
<td>151.7 ± 33</td>
<td>-33.4</td>
<td>0.001</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>6.42</td>
<td>5.89</td>
<td>-8.2</td>
<td>n.s</td>
<td>5.39</td>
<td>-16</td>
<td>n.s</td>
<td>5.04</td>
<td>-21.4</td>
<td>0.001</td>
<td>4.48</td>
<td>-30</td>
<td>0.001</td>
</tr>
<tr>
<td>GFR</td>
<td>38 ± 12</td>
<td>38.1 ± 16</td>
<td>0.26</td>
<td>n.s</td>
<td>38.5 ± 17</td>
<td>1.31</td>
<td>0.001</td>
<td>38.6 ± 16</td>
<td>1.57</td>
<td>0.001</td>
<td>38.8 ± 11</td>
<td>2.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Albuminuria: negative

744 patients with GFR (glomerular filtration rate) calculated at 38 ± 12 mL/min/m².

The percent variation (Δ%) and mean changes (mg/dL ± SD) in plasma lipid and lipoprotein profile and GFR, at baseline (T0), after 6 (T6), 12 (T12), 18 (T18) and 24 (T24) months treatment with Dif1stat®.

HDLC: high density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; TC: total cholesterol; non-HDL-C: non high density lipoprotein-cholesterol; TG: triglycerides; n.s = not significant; n/a = not applicable; P value ≤ 0.001.

Median age of 71.8 ± 11 years, with severe stage IV CKD (GFR 19 mL/min/1.73m²) (Table 1). After 6 months of treatment no statistically significant variations were noted with regard to TC (-12%), HDLC (-11%), TG (-16%), LDL-C (-11.7), TC/HDL-C (-0.56%), non-HDL-C (-12%) and GFR (+0.52%). After 12 months, the change in HDLC (+2.8%) was not significant, while the variations of TC (-23%), TG (-31%), LDL-C (-23%) non-HDL-C (-26.8%), TC/HDL-C (-25.2%) and of GFR (+1.31%) were statistically significant for P < 0.001. After 18 months, the change of HDLC (+9.1%) was not significant, while variations of TC (-26%), TG (-36%), LDL-C (-27%), non-HDL-C (-31.8%), TC/HDL-C (-32.4%) and of GFR (+2%) were statistically significant for P < 0.001. After 24 months, HDLC (+13%) was not significant, while TC (-32%), TG (-38%), LDL-C (-35%), non-HDL-C (-38.5%), TC/HDL-C (-40%), and GFR (+2.1%) were statistically significant for P < 0.001 (Table 4 and Figs. 3, 4).

4. Discussion

When renal function is compromised, lipid and lipoprotein profile changes are more evident. The lipid and lipoprotein profile alteration can worsen the mechanisms of CKD progression creating a secondary dyslipidemia which exposes the patient to an increase of cardiovascular risk from the onset of renal...
insufficiency [23]. Thus, consistent motivations exist
to begin a lipid-lowering treatment of secondary
dyslipidemia due to compromised renal function.
Studies based on limited cases, and a meta-analysis of
these studies, demonstrated that an improvement of
lipid profile helps in order to preserve the renal
function, and reduce proteinuria. More recently, it has
been reported that the progression of chronic kidney
damage can be slowed, and proteinuria reduced by
lipid-lowering treatment [24]. Even more, notes are
the results of a meta-analysis by Douglas et al. [25]
who stratified the benefit of lipid-lowering treatment
based on the severity of albuminuria. These studies
demonstrate that the effects of treatment on patients
with normal renal function are irrelevant. However,
when chronic kidney damage and increase of
microalbumin are evident the administration of
lipid-lowering drugs which reduces circulating plasma
proteins, helps in slowing the progression of kidney
damage [the TNT (Treating to New Targets) study]
[26]. In addition, recent studies confirm the efficacy of
lipid-lowering therapy in patients with CKD, as they
create an important benefit with regard to major
cardiovascular endpoints, and these advantages are, in
fact, superior to those observed in patients with
normal kidney function [27]. A non-pharmaceutical,
nutraceutical treatment was administered to the
patients considered for this study, which, paired with a
special diet, contributed to an improved plasma lipid
and lipoprotein pattern. No patient showed at the end
of the study a worsening of kidney function as
expressed by GFR level, or the appearance of
albuminuria compared with the values observed at the
beginning of treatment. Therefore, it was not
necessary to interrupt the lipid-lowering treatment
with the nutraceutic (Dif1stat®) in any patient (Figs. 1,
2, 3). In conclusion, as illustrated in Fig. 4, as soon as
the lipid-lowering treatment is begun, without
modifying the dose of nutraceutic, on patients with
CKD, the better the results are as far as the lipid and
lipoprotein profile is concerned. Patients with Stage II
CKD showed a reduction of LDLC of -42% and a
reduced progression of renal damage of +1.7
mL/min/1.73m² compared with patients on Stage III
of CKD, who showed a -33% decrease of LDLC and a
reduced progression of renal damage of 0.8
mL/min/1.73m² compared with patients on Stage IV
of CKD, who had a -35% decrease of LDLC and a
reduced progression of renal damage of 0.42
mL/min/1.73m² (Fig. 4). On the light of previously
reported evidence confirmed by our study, the
antatherogenic plasma lipid and lipoprotein profile
improvement is associated with a reduction of the
progression of renal chronic damage. The non-pharmaceutical treatment, which is far favorable
to drug administration, additionally improves the

Table 4  Group C: Stage IV of CKD according to KDOQI classification.

<table>
<thead>
<tr>
<th>Months</th>
<th>T0</th>
<th>T6</th>
<th>Δ%</th>
<th>P</th>
<th>T12</th>
<th>Δ%</th>
<th>P</th>
<th>T18</th>
<th>Δ%</th>
<th>P</th>
<th>T24</th>
<th>Δ%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>285 ± 57</td>
<td>251 ± 29</td>
<td>-12</td>
<td>n.s.</td>
<td>219 ± 32</td>
<td>-23</td>
<td>0.001</td>
<td>210 ± 41</td>
<td>-26</td>
<td>0.001</td>
<td>193.4 ± 53</td>
<td>-32</td>
<td>0.001</td>
</tr>
<tr>
<td>HDLC</td>
<td>35 ± 19</td>
<td>31 ± 16</td>
<td>-11</td>
<td>n.s.</td>
<td>36 ± 22</td>
<td>2.8</td>
<td>n.s.</td>
<td>38.2 ± 29</td>
<td>9.1</td>
<td>n.s.</td>
<td>39.8 ± 18</td>
<td>13</td>
<td>n.s.</td>
</tr>
<tr>
<td>TG</td>
<td>222 ± 57</td>
<td>186 ± 63</td>
<td>-16</td>
<td>n.s.</td>
<td>152 ± 41</td>
<td>-31</td>
<td>0.001</td>
<td>141 ± 59</td>
<td>-36</td>
<td>0.001</td>
<td>137 ± 39</td>
<td>-38</td>
<td>0.001</td>
</tr>
<tr>
<td>LDLC</td>
<td>196 ± 71</td>
<td>173 ± 96</td>
<td>-11.7</td>
<td>n.s.</td>
<td>151 ± 85</td>
<td>-23</td>
<td>0.001</td>
<td>143 ± 94</td>
<td>-27</td>
<td>0.001</td>
<td>126 ± 45</td>
<td>-35</td>
<td>0.001</td>
</tr>
<tr>
<td>non-HDLC</td>
<td>250 ± 33</td>
<td>220 ± 42</td>
<td>-12</td>
<td>n.s.</td>
<td>183 ± 67</td>
<td>-26.8</td>
<td>0.001</td>
<td>171.8 ± 49</td>
<td>-31.8</td>
<td>0.001</td>
<td>153 ± 56</td>
<td>-38.5</td>
<td>0.001</td>
</tr>
<tr>
<td>TC/HDL</td>
<td>8.14 ± 8</td>
<td>-0.56</td>
<td>n.s.</td>
<td>6.08</td>
<td>-25.2</td>
<td>0.001</td>
<td>5.49</td>
<td>-32.4</td>
<td>0.001</td>
<td>4.85</td>
<td>-40</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>GFR</td>
<td>19 ± 6</td>
<td>19.1 ± 5</td>
<td>0.52</td>
<td>n.s.</td>
<td>19.25 ± 7</td>
<td>1.31</td>
<td>0.001</td>
<td>19.38 ± 2</td>
<td>2</td>
<td>0.001</td>
<td>19.42 ± 1</td>
<td>2.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

180 patients with GRF (glomerular filtration rate) calculated at 19 ± 6 mL/min/m².

The percent variation (Δ%) and mean changes (mg/dL ± SD) in plasma lipid and lipoprotein profile and GFR, at baseline (T0), after
6 (T6), 12 (T12), 18 (T8) and 24 (T24) months treatment with Dif1stat®

HDLC: high density lipoprotein-cholesterol; LDLC: low-density lipoprotein-cholesterol; TC: total cholesterol; non-HDLC: non high
density lipoprotein-cholesterol; TG: triglycerides; n.s. = not significant; n/a = not applicable; P value ≤ 0.001.
compliance of the patient. It is also to be taken into consideration that these particular patients undergo a consistent poly-pharmaceutical treatment. The treatment with nutraceutics, as a matter of fact, showed evidence of lipid-lowering efficacy, with reduced side effects. The use of Diflstat® in the treatment of secondary dyslipidemia in patients with CKD showed, with reasonable safety in assumption, an improvement of lipid profile which, as already noted in literature, is able at reducing the progression of CKD. Although these findings are mainly of observational nature, they confirm existing evidence of the benefit of the assumption of lipid-lowering agents in the treatment of CKD (Figs. 1, 2, 3). Further investigational studies are needed not only to confirm the outcome of this study, but also to compare the efficacy and safety of different lipid-lowering agents given for dyslipidemia when associated to CKD.

5. Conclusion

The relationship between dyslipidemia and CVD in the general population is strong indeed, and universally recognized. Dyslipidemia is also a common clinical finding amongst patients with CKD. However, lipid-lowering therapy is not widely used in subjects with CKD despite the evidence that this population is at high risk of developing CVD, the leading cause of death amongst these patients, particularly when they have end-stage disease. Dyslipidemia in patients with CKD is very often represented by elevation of TG and reduction in HDLC levels. Treatment with fibrates would seem a reasonable therapeutic approach, but evidence is scarce. It is well-known that statins use, which would be helpful in reducing cardiovascular events, and it has been also suggested that statins may slow the progression of CKD. However, it is unclear whether the supposed favorable renal effects of statins are due to the reduction of plasma cholesterol levels and/or their pleiotropic activity. Moreover, doubts about the safety of statin administration in CKD patients have been raised. Therefore, there has been uncertainty as to whether lipid-lowering therapy should be given safely to patients with CKD. Nutraceuticals (monacolin, policosanol, red yeast rice) are claimed to have a favourable impact on CVD through the reduction of plasma LDL and TG levels. Further randomized, controlled studies are needed to support the scientific evidence for the administration of nutraceuticals both in prevention and as treatment for CVD. This is also the case for nutraceuticals given to patients with CKD in whom a dyslipidemia is clinically demonstrated. This must be recognized. Notwithstanding, the assumption that lipid-lowering therapy is helpful in the aforementioned patients to prevent CVD, gives support to the use of Diflstat® in this setting. In our opinion our findings confirm previous reported evidence on efficacy and safety of Diflstat® in the treatment of moderate dyslipidemia. In the light of our results this is also conceivable as far as the clinical management of dyslipidemia associated to CKD is concerned.

References


