Clinical Science

Insulin Resistance and Metabolic Syndrome in Hepatitis C Virus Seronegative Heroin Dependents

Zanina Pereska1, Danijela Janicevic-Ivanovska2, Natasa Simonovska1, Aleksandra Babulovska1, Aneta Trajanovska-Spasovska1, Kiril Naumoski2, Kristin Kostadinoski2

1 University Clinic for Clinical Biochemistry Skopje; Goce Delchev University-Shtip, Republic of North Macedonia
2 University Clinic for Toxicology; Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia

Abstract

Initial studies on impaired glucose-insulin homeostasis in heroin dependents have not defined the impact of concomitant hepatitis C infection (HCV), which has been strongly associated with the development of insulin resistance and metabolic syndrome (MS). The aim of our study was to evaluate the association of heroin dependence with glucose-insulin homeostasis disturbances and MS in heroin dependents with HCV seronegativity. Materials and methods: The study was prospective and cross-sectional, including 160 heroin dependents compared to a control group of 60 participants. MS was diagnosed using International Diabetes Federation criteria. The homeostatic model assessment for insulin resistance (HOMA-IR) and pancreatic β-cell function (HOMA-%B) were used for assessing insulin resistance and β-cell function of pancreas. Results: MS was detected in 9.32% of heroin addicts. Heroin dependents with MS compared to dependents without MS were older, had higher BMI, waist circumference and significantly higher systolic and diastolic blood pressure, increased triglycerides (F=8.233, df=2, p=0.001), insulin resistance-HOMA-IR (F=4.928, df=2, p=0.001), and reduced HDL-C (F=25.926, df=2, p<0.001) and apoA-I (F=16.406, df=2, p<0.001), significantly increased insulinemia (F=4.928, df=2, p<0.001), insulin resistance-HOMA-IR (F=4.928, df=2, p=0.005) and insignificantly increased pancreatic β-cell function (F=2.461, df=2, p=0.05). Conclusions: Insulin resistance and MS, independent of HCV, was also registered in heroin dependence. Timely recognition will enable more successful treatment of comorbidities and illicit drug depence.


Key words: heroin dependents, metabolic syndrome, insulin resistance, HOMA-IR, HOMA-%B

Correspondence: Zanina Pereska, University Clinic for Toxicology; Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia. E-mail: perevska@yahoo.com

Received: 7-Oct-2023; Revised: 17-Dec-2023; Accepted: 21-Dec-2023

Copyright: © 2023. Zanina Pereska, Danijela Janicevic-Ivanovska, Natasa Simonovska, Aleksandra Babulovska, Aneta Trajanovska-Spasovska, Kiril Naumoski, Kristin Kostadinoski. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

Competing Interests: The author have declared that no competing interests

Извадок

Приначните студии на нарушената глукозно-инсулиновата доместоза при heroin зависности не го дефинираа и влијанието на хепатитис Ц инфекцијата (ХЦИ), каде се ефективно поврзана со развој на инсулинска резистенција и метаболички синдром (МС). Целата на нашата студија беше да ја процени поврзаноста на зависимоста од heroin со нарушението на глукозно-инсулинската доместоза и МС кај heroin зависности кои се ЗДВ серонегативни. Материјал и методи: Студијата беше проспективна и пресечна, вклучувајќи 160 heroin зависности и контролна група од 60 испитаници. МС беше дијагностициран според критериите на Меѓународната федерација за дијабетес. За проценка на инсулинската резистенција и функцијата на β-клетките на панкреасот беше користен модел на инсулинска резистенција (HOMA-IR) и функцијата на β-клетките на панкреасот (HOMA-%B). Резултати: МС беше детектирана кај 9,32% од зависимите и тие во споредба со зависимите без МС без погста, со повисок БМА, обем на половината и значително повисок систолен и диастолен крвени притисок, значително повисоки трглицериди (F=8,233, df=2, p=0,001), хомеостатски модел за инсулинска резистенција (HOMA-IR) и функцијата на β-клетките на панкреасот (HOMA-IR). Зависностите и МС, независно од ХЦИ инфекција, се регистрираа и кај heroin зависностите. Навременоот преознаане ќе овозможи пошумен третман на коморбидитетите и на болеста на зависноста од илегални дроги.
Introduction
The research interest in heroin dependence (HD) and associated complications in the last decades has been focused on studying the metabolic disturbances along with the infectious complications. During the ‘90s of the 20th century, the metabolic derangements in HD were investigated through the glucose metabolism which presented diabetic type 2 of glucose utilization, thus insulin resistance (IR) was speculated; performing the hyperinsulinemic euglycemic glucose (HIEG) clamp technique as a golden standard for detecting IR was inapplicable for this population group due to their low compliance. Later, lipid metabolism disorders as hypertriglyceridemia and low HDL-C in HD were reported. At the beginning of the 21st century the presence of metabolic syndrome (MS) was shown in opioid dependents. There were reports of cardiovascular complications, rheological disorders, reduced central arterial elasticity in HD, and complications usually associated with MS in the general population. Among the most common comorbidities in HD was chronic hepatitis C virus infection, which was significantly associated with IR leading to type 2 diabetes mellitus and MS. So far, the reports that have analyzed the metabolic disturbances in HD have not assessed the influence of HCV infection on IR, lipid disorders and MS.

However, IR and MS have also been significantly associated with cognitive and psychiatric disorders, especially depression as very common comorbidities in HD, which may have a particular impact on heroin dependents who report in detoxification or substitution programs and may affect their motivation for treatment.

The aim of our study was to evaluate the association of heroin dependence with glucose-insulin homeostasis disturbances and MS in heroin dependents with HCV seronegativity.

Materials and methods
The study had a prospective cross-sectional design and enrolled 160 opiate dependents and 60 healthy controls, all cigarette smokers, who previously signed written informed consent for participation in the study. The study was approved by the Ethics Committee of the Faculty of Medicine in Skopje. Blood samples and urine were taken at the moment of patients’ admission to the University Clinic for Toxicology for introducing buprenorphine substitution therapy. Only patients who obeyed the recommendation for night and morning fasting before admission to the Clinic were analyzed. The inclusion criteria were: 1) heroin dependence lasting minimum one year (diagnosed according to International Classification of Diseases-Classification of Mental and Behavioral Disorders –Clinical Description and Diagnostic Guidelines, 11th revision (ICD 11), 2) reference BMI (18.5–24.9 mg/m2). Exclusion criteria were: 1) use of psychostimulant substances in
the last 7 days, 2) history of obesity, 3) family history of diabetes, 4) history of hyperuricemia, 5) use of anti-inflammatory drugs in the last 7 days (NSAID, steroids, salicylates), 6) acute infectious or chronic disease, 7) use of antioxidants in the last 4 weeks, 8) HIV, hepatitis B or C infection seropositivity, 9) more than twofold increase in aminotransferase level over the upper reference range.

The following clinical and paraclinical investigations were performed: 1) anamnesis and physical examination, including unstandardized questionnaire adapted according to Addiction Severity Index, 5th edition, 2) standard biochemical and toxicological analysis, 3) C-peptide measurement (chemiluminescence immunoassay (immunology analyzer IMMULITE 2000), expressed in ng/ml), 4) Brinkman Index – a mathematical model for the estimation of cumulative index of smoking yield by multiplying number of smoked cigarettes per day and years of smoking12, 5) lipid status: triglycerides (TGl), high-density cholesterol (HDL-C), low density cholesterol (LDL-C) (enzymatic colorimetric test on an INTEGRA 400 autoanalyzer, Roche) and apolipoprotein A (ApoA-I) and apolipoprotein B (apoB) (immunoturbidimetric method, autoanalyzer INTEGRA 400), 6) IR was calculated using homeostatic models for assessment of IR (HOMA-IR) and beta cell function (HOMA-%B) by Mathews DR. This mathematical model uses values of fasting glycemia (mmol/l) and fasting insulinemia (μU/ml) to calculate IR (IR): HOMA-IR=(FPIxFPG) / 22.5 and beta cell function: HOMA-%B= (20 xFPI) x (FPG -3.5)13. Insulinemia was determined by MEIA (microparticle enzyme immunoassay) μU/ml, 7) Clinical criteria of International Diabetes Federation (IDF) for assessing MS were used14. Waist circumference was measured midway between rib arch and superior iliac spine on the same side at the end of normal expiration in a standing position. Waist circumference critical value for European males is ≥94 cm and for European females is ≥84 cm and plus the presence of any two of the following four factors: a) TGl ≥1.7 mmol/l or specific treatment for this lipid abnormality, b) HDL-C (m) ≤1.03 mmol/l and HDL-C (f) ≤ 1.29 mmol/l or specific treatment for this lipid abnormality, c) blood pressure ≥130/85 mmHg or treatment of previously diagnosed hypertension were measured by trained staff using standardized protocols), d) glycemia ≥5.6 mmol/l or previously diagnosed type 2 diabetes.

Statistical analysis

The results obtained are presented as mean±SD, frequencies and percentages. Continuous variables were compared using Student’s t test and one-way analysis of variance (Tukey). Categorical variables were compared using the Chi-square test. The association of HOMA-IR with the independent variables (predictors) and the associated influence of the independent variables on HOMA-IR were assessed with the multiple regression analysis. P val-
values less than 0.05 were considered to be statistically significant. Data were analyzed using the SPSS/Win program (version 25).

Results

The study enrolled 220 participants - 160 heroin dependents (HDs) and 60 controls. MS was registered in 9.32% of HD. Also, 17.1% of HDs who did not have MS defined by these criteria, had increased waist circumference. HDs were divided into two groups of subjects: subjects with MS according to the IDF criteria (HDM+) and subjects where the criteria for MS were not met (HDM-) (Table 1).

HDM+ compared to HDM- and the control group were significantly older (F=3.698, df=2, p<0.05), with higher BMI but in reference range (F=9.874, df=2, p<0.001), with larger mean waist circumference (F=22.548, df=2, p<0.001), higher mean systolic (F=7.923, df=2, p<0.001) and mean diastolic blood pressure (F=7.597, df=2, p=0.001), higher mean TGl (F=8.233, df=2, p<0.001). There were significantly lower mean HDL-C and significantly lower apoA-I in HDM+ compared to HDM-, but both groups showed significantly lower values of HDL-C (F=25.926, df=2, p<0.001) and apoA-I (F=16, 406, df=2, p<0.001) compared to the control group. However, there was significantly higher apoB (F=8.154, df=2, p=0.001) in HDM+ compared to HDM- group (Table 1).

Carbohydrate profile showed no significant difference in glycemia (F=1.497, df=2, p>0.005) as opposite to the higher values of insulin (F=4.667, df=2, p<0.05) and HOMA-IR (F=4.928, df=2, p<0.05) and in significantly higher HOMA-%B (F=2.461, df=2, p<0.05) and C-peptide (F=1.389, df=2, p>0.05) in HDM+ compared to HDM- group (Table 1).

There was no significant difference between HDM+ and HDM- group in heroin dependence duration (t=-0.140, DF=158, p>0.05), but HDM+ had higher Brinkman index (F=4.389, df=2, p<0.05). The difference in gender distribution between HDM+ and HDM- was insignificant (χ²=0.419, DF=1, p>0.05), but it was significant in comparison to controls (χ²=7.230, df=2, p<0.05). Males were predominant in HD group (χ²=11.267, df=1, p<0.05). Inhalation and intravenous route of drug administration showed a similar distribution in both HDM+ and HDM- groups (χ²=0.473, DF=1, p>0.05) (Table 1).

Table 1. Mean values of the observed variables in heroin dependents with and without MS and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>HDM (-)</th>
<th>HDM(+)</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=145</td>
<td>N=15</td>
<td>N=60</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.87± 5.78</td>
<td>31.27 ± 5.775*</td>
<td>29.89 ± 6.200</td>
</tr>
<tr>
<td>Gender (m/f)%</td>
<td>87.7% / 12.3%</td>
<td>93.3% / 6.7%</td>
<td>73.8% / 26.2% ^.*</td>
</tr>
<tr>
<td>Route of drug administration (inh/I.V.)</td>
<td>49.3% / 50.7%</td>
<td>40% / 60%</td>
<td>/</td>
</tr>
</tbody>
</table>
When determining the predictors for MS in HD, the joint influence of predictor variables was tested: age, duration of heroin addiction, waist circumference, Brinkmann index, BMI, HOMA-IR, HOMA-B, TGl, HDL-C, diastolic and systolic blood pressure, glycemia and gender. The independent variables (duration of HD, Brinkmann index, BMI, HOMA-%B, age, HDL-C, diastolic and systolic blood pressure, glycemia and gender) did not have a statistically significant influence as predictors for MS in the group of HD. Waist circumference is a variable with the greatest predictive value, where an increase of 1 cm in waist circumference increases the risk of metabolic syndrome by 3.12 (95%CI 1.41 – 6.89). The next significant risk factor is HOMA-IR since with each unit increase, the risk of MS increases by 1.5(95%CI 1.02 – 2.45). An increase in the concentration of TGl by 1 mmol/l under combined influence with other predictors increases the risk of occurrence of MS by 2.38 (95%CI 1.01 – 5.61). An increase in age by one year increases the risk by 1.2 (95%CI 0.86 -1.88) for the occurrence of MS, but this effect is not considered significant (p>0.05).

All independent variables together influenced on 74.8% of MS variability, while in 25.2% of MS variability was due to the influence of other factors (Table 2).
Discussion

Our study found MS in HD who were seronegative for HCV infection and had BMI in reference range. It was detected in 9.32% of HD and was identified using the IDF criteria for clinical assessment of this syndrome. These are the first results in our country to address the issue of MS in HD who are serologically negative for HCV and HBV infection. Until now, the study of Mattoo et al. presented the occurrence of MS in alcohol and HD4 with significantly higher representation of MS (29.3%) compared to that in our study. This difference was a result of the inclusion of subjects with liver disease and diabetes, an older group of subjects (37.43 ± 10.89 years) in a significantly smaller sample of observed subjects (41 patients). Also, a high prevalence of MS was registered in the group receiving methadone maintenance therapy who were older (46.1 ± 9 years) than our subjects\textsuperscript{15}. In the study by Nebhinani N et al., the prevalence of MS in heroin dependence was 9.6%, which was very similar to the results obtained in our study\textsuperscript{16}. However, a lower sensitivity of the IDF criteria in detecting MS in HD was reported, with prevalence of 5.1% compared to 20.3% prevalence by using the revised National Cholesterol Education Program Adult Treatment Panel III guidelines\textsuperscript{17}. The prevalence of MS in the general population was significantly higher compared to our results, where 21.8\%\textsuperscript{18}, 21\%\textsuperscript{19}, 33.7\%\textsuperscript{20} and 22.6\%\textsuperscript{21} were registered, but older age groups were included and a larger number of respondents compared to our study subjects. In the study by Hildrum et al., MS de-

<table>
<thead>
<tr>
<th>Metabolic syndrome</th>
<th>p</th>
<th>OR</th>
<th>95% CIa OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference(cm)</td>
<td>0.005</td>
<td>3.125</td>
<td>1.416</td>
</tr>
<tr>
<td>TGl(mmol/l)</td>
<td>0.046</td>
<td>2.386</td>
<td>1.015</td>
</tr>
<tr>
<td>HDL-C(mmol/l)</td>
<td>0.809</td>
<td>0.578</td>
<td>0.007</td>
</tr>
<tr>
<td>Glucose(s) [mmol/l]</td>
<td>0.163</td>
<td>0.278</td>
<td>0.046</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>0.987</td>
<td>1.002</td>
<td>0.815</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>0.541</td>
<td>1.103</td>
<td>0.805</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.226</td>
<td>1.274</td>
<td>0.861</td>
</tr>
<tr>
<td>Duration of HD (years)</td>
<td>0.722</td>
<td>1.089</td>
<td>0.680</td>
</tr>
<tr>
<td>HOMA – IR</td>
<td>0.043</td>
<td>1.821</td>
<td>1.018</td>
</tr>
<tr>
<td>HOMA- %B</td>
<td>0.160</td>
<td>0.993</td>
<td>0.984</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>0.391</td>
<td>0.005</td>
<td>0.000</td>
</tr>
<tr>
<td>BMI kg/m2</td>
<td>0.757</td>
<td>0.892</td>
<td>0.408</td>
</tr>
<tr>
<td>Brinkman index</td>
<td>0.692</td>
<td>0.997</td>
<td>0.980</td>
</tr>
<tr>
<td>Const</td>
<td>0.005</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

Method: Enter:.; -2 Log likelihood:27 500; Nagelkerke R2: 0.748, OR- odds ratio
ected in line with the IDF criteria in a younger population group of Europeans aged 20-29 years was found in 9-11% of subjects, which was considered as a high prevalence for this age group, and corresponded to the prevalence of MS in our subjects. MS is associated with an increased risk of cardiovascular diseases and events; has its own special significance in heroin dependence, considering the fact that cardiovascular diseases appear to be a more significant cause of morbidity and mortality compared to infectious diseases in this population group, i.e., cardiovascular events were on the third place as a cause of mortality (0.17%) in this population group and on the fourth place (9.4%) as a factor that contributed to the shortening of life during the evaluation using the “years of potential loss of life” method in HD.

There are many reports about the association of MS with IR. In our study, glycemia was insignificantly higher in HDM+ in contrast to significantly increased insulinemia and HOMA-IR in HDM+ compared to MSD-, implying IR in HD. There is an increasing number of reports that have explained the complex mechanism of IR, some of them even including the effects of opioids, like influence on receptor levels, transport molecules, adipocyte hormones as well as influence on insulin-degradation enzymes. Desensitization of insulin signaling through μ-opioid receptors by enhancing serine 612 phosphorylation of the insulin receptor supstrate-1 (IRS-1 Ser612), as well as other serine residues, resulted in dissociation of the insulin receptor from its main adapter signaling complexes and reduced activity. The mechanism of chronic intermittent hypoxia as a very common phenomenon in HD also reduces GLUT4 (glucose transporter 4) activity, thus inducing IR in peripheral tissues. The excess of free radicals and low concentration of antioxidants, which have already been observed in chronic heroin use, induced reduced GLUT4 activity, too. Additionally, the low levels of adiponectin in heroin dependence were associated with IR independently of body weight and adipose tissue.

Disturbed nutrition and its composition can affect glucose regulation primarily due to the zinc deficiency observed in HD, and the decrease in zinc concentrations was linear to duration of heroin use observed in a study in a 6-year period. The insulin degrading enzyme, as a metalloprotease, contains zinc which is essential for the enzyme’s catalytic activity. Zinc deficiency, in proportion to the duration of heroin dependence, would reduce the activity of the insulin-degrading enzyme during long-term heroin use and thus may cause reduced degradation of the hormone besides the desensitizing effect of heroin metabolites on insulin receptors and the induction of IR. Given the fact that C-peptide and insulin are produced in equimolar concentrations, this mechanism can be associated with our finding of significantly higher HOMA-IR with non-significantly higher basal values of C-peptide.
and HOMA-%B in HDM+ compared to HDM- and the group of healthy subjects, implying a reduced insulin clearance as one of the mechanisms for sustained increased insulinemia with IR.

Inflammation and inflammatory mediators are one of the first observed key factors associated with IR and MS as a proinflammatory condition. Heroin and morphine, as an active metabolite of heroin, in immunomodulatory manner can affect IR by changing the levels of certain cytokines. These include morphine-stimulated elevation of interleukin (IL)-6 levels\textsuperscript{35}, thereby inducing IR through ubiquinone-mediated IRS-1 degradation. In one study, under the influence of heroin, concentrations of IL-10 that supported insulin sensitivity decreased\textsuperscript{36}. Increased IL-6 and decreased IL-10 levels participate in the development of muscle and hepatic IR. These findings can be empirically supported when insulin response in HD was improved with salicylates administration\textsuperscript{37}.

The increased blood pressure is an important criterion in defining MS. The mean systolic and diastolic blood pressure in our subjects did not reach anticipated values for hypertension, but they were significantly higher in HDM+ compared to HDM-. This has also been reported by other authors\textsuperscript{4,16,17,38}. The association of IR and MS was reported as a result of impaired renal sodium metabolism, renin-angiotensin-aldosterone, sympathetic nervous systems\textsuperscript{39} and endothelial dysfunction\textsuperscript{40}.

In our study, HDM+ were significantly older and with higher BMI, waist circumference, higher TGl, decreased HDL-C, apoA-I, and increased apoB.

Several longitudinal studies have shown that patients with MS are at increased risk of cardiovascular complications regardless of their BMI\textsuperscript{41,42}. Hence, BMI subphenotypes have been defined as metabolic-obese normal weight individuals (normal BMI, increased IR, increased central obesity and with all clinical parameters of MS, 3-28\% of observed population), and metabolically healthy obese individuals who, despite a BMI over 30 kg/m\textsuperscript{2}, are insulin sensitive and not exposed to cardiovascular risk, represented by 11-28\%. The representation of MS in HD in our study falls within the range of the group of metabolic-obese individuals with normal weight and monitoring of clinical parameters for MS should be the same as in the general population.

Dyslipidemia profile in HDM+ in this study was characterized by increased TGl, apoB, and decreased HDL-C and apoA-I concentrations. Increased TGl with decreased HDL-C have been described in studies investigating MS in HD\textsuperscript{4,16,17,38}. At the same time, increased TGl are among the most common registered disorders in MS in this population group, but the association with HCV infection was not investigated\textsuperscript{17,38,43}. Studies that report the effect of heroin on biochemical parameters associate this phenomenon with morphine direct effect of decreased li-
polytic activity in adipocytes, which gradually reaches a level of toler-
ance. From a clinical point of view, an important mechanism that in-
duces an increase in the concentra-
tion of TGI are episodes of hypoxia, common in heroin use, which in-
creases the level of TGI by reducing its clearance.

A significant reduction in HDL-C concentrations has been described in several studies. Wilcheck et al. explained the low HDL-C as result of the liver lesion in their group of dependents. Maccari et al. observed decreased levels of HDL-C in HD with normal BMI, which is in agreement with our results. However, they did not define the prevalence of HCV infection, but only the correlation with ALT, which in their case was negative. In contrast, our results in HDs were with no pathological findings on abdominal ultrasound, seronegative findings for HCV infection and no more than twofold elevated aminotransferases. The decreased level of adiponectin, noted also in HD, was significantly associated with the occurrence of the combination of lipid disorders of the type of hypertriglycerideremia with a decrease in HDL-C, independent of intra-abdominal obesity and insulin resistance. Hypoadiponectinemia also correlates with an increased hepatic lipase activity increasing the catabolism of HDL-C and apoA-I. Of course, cigarette smoking and alcohol are significant mechanisms that participate in less than 50% of the variation of HDL-C values in the general population and in the popu-
lation of HD, in addition to TGI, cholesterol and IR. Considering the protective functions of apoA-I and HDL-C, several controlled epidemiological studies have confirmed the existence of a significant inverse association between HDL-C and its major lipoprotein ApoA-I with a high cardiovascular risk and atherosclerosis. In our study, HDM+ had significantly higher levels of apoB compared to HDM- and these levels were insignificantly higher compared to the index value in the control group. The apoB was considered as the most significant marker of the atherogenic potential in the body and strongly correlated with the ultrasonographic finding of atherosclerotic changes of blood vessels and the occurrence of MS in the general population. The presented apolipoprotein levels in HDM+ group could be partially explained by the significantly increased cumulative index of cigarette smoking, Brinkman index, i.e., decreased apoA-I with increased apoB profile was associated with cigarette smoking.

Identifying HD with IR and MS may serve as a criterion for recommending the type of substitution program (methadone or buprenorphine) taking into consideration the reports where patients on buprenorphine substitution program presented better metabolic profile compared to methadone.

**Conclusion**

Heroin dependence does not exclude the association of opioid use with IR and MS, independently of BMI and
HCV infection. Timely recognition of IR and MS and treatment of HD can increase the success in reducing comorbid complications, can help in recommending the type of substitution therapy, thereby indirectly contributing to more successful dependents' rehabilitation and better quality of life.

References


