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ARTICLES

Case Report

A novel RAB-27A mutation causing Griscelli syndrome type 2 with severe central nervous system involvement: Case report and review of literature
Ali M. Alsuheel, Ayed A. Shati, Amer A. Alshehri and Mansour Y. Otaif

Research Articles

Cryptosporidium parvum and its association to risk of malnutrition in school children of Northwest Mexico: A brief report
Carmen María Lugo Flores, Jose Luis López Villalobos, Gloria Guadalupe Morales-Figueroa, Julián Esparza Romero, Jose Antonio Ponce Martinez, Martín Guadalupe López Sañudo and Luis Quihui-Cota

Impact of intervention on knowledge and risk factors of coronary heart disease among teachers in Sokoto, Nigeria
Awosan K. J, Ibrahim M. T. O, Makusidi M. A, Essien E and Adeniji A

Psycho-immunological rehabilitation of advanced cancer patients with psychogenic medical history
Oleg V. Bukhtoyarov and Denis M. Samarin

Sun avoidance among indoor employees leading to vitamin D deficiency and depression in the United Arab Emirates
Fatme Al-Anouti, Sumaya Al-Ameri, Justin Thomas, Laila Abdel-Wareth, Subashnie Devkaran, Jaishen Rajah and Afrozul Haq
Case Report

A novel RAB-27A mutation causing Griscelli syndrome type 2 with severe central nervous system involvement: Case report and review of literature

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Griscelli syndrome (GS) is one of the rare autosomal recessive disease characterized by hypopigmentation of the hair, hepatosplenomegally, primary immunodeficiency and neurological manifestations. It was described by Griscelli et al. (1978) in France, who reported two girls who were presented with silver gray hair, several episodes of fever, hepatosplenomegally and pancytopenia. There are three types of Griscelli syndrome based on clinical features and genetic mutations. We report a five month old girl diagnosed as Griscelli syndrome type 2 (OMIM #607624) presenting with significant central nervous system involvement. The molecular studies of the RAB27A gene were performed. Coding sequence revealed a novel homozygous deletion at (c.138delC). In communities with high incidence of consanguineous marriages, we should keep in mind the rare primary immunodeficiency diseases with autosomal recessive inheritance. Early diagnosis and treatment will help in improvement of the outcome.

Key words: Griscelli syndrome type 2, RAB27A, CNS involvement.

INTRODUCTION

Griscelli syndrome is one of the rare autosomal recessive disease characterized by hypopigmentation of the hair, hepatosplenomegally, primary immunodeficiency and neurological manifestations. It was described by Claude Griscelli and Michel Prunieras in 1978 in France, who reported two girls who were presented with silver gray hair, several episodes of fever, hepatosplenomegally and pancytopenia (Griscelli et al., 1978; Tomita and Suzuki, 2004; Rezaei et al., 2009; Klein et al., 1994; Ménasché et al., 2000). We report a 5 month old girl with seizure, silvery grey hair and hepatosplenomegally which fulfill features of Griscelli syndrome type 2 and confirmed by gene study with a novel gene mutation.

CASE REPORT

A 5-month-old Saudi female infant, the first child of consanguineous parents (first cousins). The patient’s past medical history was uneventful until the age of 5 months, when she was referred to Aseer Central
Hospital, a tertiary referral center in Aseer region, Saudi Arabia, because of fever, right focal seizure and abdominal distension. Physical examination revealed silvery grey hair, eyelashes, eyebrows (Figure 1) and hepatosplenomegaly (liver and spleen were palpable below costal margins 4 cm and 3 cm, respectively).

Laboratory data revealed white blood cell count of 6650/µL; (polymorphonuclear cells, 28%; lymphocytes, 60%; monocytes, 12%); hemoglobin, 11.3g/dL and platelet count, 396×103/µL. The erythrocyte sediment rate was 15 mm/h, C-reactive protein was negative and all septic workup cultures including blood and CSF were negative upon admission. The peripheral blood smear showed no giant cytoplasmic granules in leukocytes. The results of biochemical tests were as following: alanine aminotransferase, 16 IU/L (normal range, 10-40); aspartate aminotransferase, 64 IU/L (normal range, 10-40 IU/L); lactate dehydrogenase, 532 IU/L (normal range, up to 450 IU/L); total bilirubin, 0.2mg/dL (normal range, 0.2-1 mg/dL); direct bilirubin, 0.1mg/dL (normal range, 0-0.2 mg/dL). Triglyceride level was 253 mg/dL (normal range, 35-200 mg/dL) and ammonia level was 84ng/mL (normal range, 16-60 ng/mL). Metabolic screening was unremarkable.

The chest x-ray was normal, although abdominal ultrasound revealed hepatosplenomegaly. Brain MRI showed severe cerebral edema with multiple brain parenchymal hematomas and dural sinus thrombosis. Microscopic examination of the hair showed irregular agglomerations of pigment in the hair shafts (Figure 2). The electroencephalogram was done and it showed continuous slow activity with severe degree of encephalopathy. The patient was started on chemotherapy but she did not respond and she developed stormy hospital course with multiple medical problems including VRE (Vancomycin-resistant Enterococcus) meningoecephalitis/encephalopathy, seizure disorder, uncontrolled hypertension, severe pneumonia, CMV and urinary tract infections infection. The patient was seen by Neurology and Neurosurgical teams and they decided that it may not be safe to do lumbar puncture and administer intrathecal chemotherapy for her CNS illness, due to the severely raised intracranial pressure. No surgical intervention was recommended by Neurosurgeon. Unfortunately, the patient continued to deteriorate till she passed away after two weeks of admission. The patient was diagnosed with Griscelli syndrome type 2 with severe central nervous system involvement based on characteristic hair finding, neuroimaging studies and molecular genetics study (Figure 3). Her parents were referred to genetic counseling for future pregnancies.

**DISCUSSION AND LITERATURE REVIEW**

Griscelli syndrome is a rare and potentially fatal autosomal recessive disease. Pigment dilution of hair, skin, eyelashes and eyebrows. Immunologic and neurologic abnormalities associated with hepatosplenomegaly and recurrent infections are the general features of GS (Kurugöl et al., 2001). Three types of Griscelli syndrome have been identified. Silvery gray hair is common to all three, but immunological defects are only seen in the patients with Griscelli syndrome type 2 (Griscelli et al., 1978; Tomita and Suzuki, 2004; Rezaei et al., 2009) while the neurological manifestations are common in Griscelli GS type 1.

This syndrome is a rare inherited disorder that was originally described in 1978 (Griscelli et al., 1978). In 1997, Pastural et al. (2000) found a homozygous mutation of the gene encoding myosin VA protein (MYO5A) in a Turkish girl with Griscelli syndrome. In 2000, the same author presented evidence indicating the existence of a second locus associated with GS in the 15q21 region, which is located in less than 7.3 cm from...
the MYO5A gene, the RAB27A gene7. Currently, GS is classified into 3 types based on the genetic and molecular features. GS 1 is described as silvery gray hair, severe psychomotor delay which are related to MYO5A gene. Griscelli syndrome types 1 and 3 are caused by mutations in the MYO5A and MLPH genes, respectively, while type 2 is caused by mutations in RAB27A (Ménasché et al., 2000; Wilson et al., 2000; Ménasché et al., 2003).

Oculocutaneous hypopigmentation may be associated with primary immunodeficiency diseases involving immune dysregulation. In addition to Griscelli syndrome, Chediak-Higashi syndrome (caused by a mutation in the LYST gene), Hermansky-Pudilak syndrome type 2 (caused by a mutation in the AP3B1 gene) and p14 deficiency (caused by a mutation in the MAPBPIP gene) are other autosomal recessive immunodeficiency diseases associated with oculocutaneous hypopigmentation (Rezaei et al., 2009; Speckmann et al., 2008). Although patients with these mutations may have similar phenotypes, laboratory findings such as regular melanin granules (Chediak-Higashi syndrome), large irregular melanin granules (Griscelli syndrome) and giant neutrophilic granular inclusions in peripheral blood leukocytes (Chediak-Higashi syndrome) can help to confirm the clinical diagnosis (Rezaei et al., 2009; Speckmann et al., 2008). However, the definitive diagnosis can only be made after molecular analysis, once the mutation has been identified.

Our patient had the typical clinical features of Griscelli syndrome type 2. She presented with seizures, hepatosplenomegaly, pancytopenia and silvery hair. Microscopic examination of hair showed large irregular pigmentation. These features are typical for Griscelli syndrome type 2. The molecular genetics confirmed that she has a novel gene mutation that has not been reported previously, molecular study sequencing revealed a novel homozygous deletion at (c.138delC). The prognosis of Griscelli syndrome type 2 is poor and patients usually die in early childhood with complications such as hemophagocytic lymphohistiocytosis, unless they undergo hematopoietic stem cell transplantation (Klein et al., 1994). Although this is the only curative treatment for patients with Griscelli syndrome type 1 and type 2 (Klein et al., 1994), hemophagocyticlymphohistiocytosis should be treated first to induce remission before transplantation (Henter et al., 2010; Janka, 2007).

**Conclusion**

In communities with high incidence of consanguineous marriages, we should keep in mind a rare primary immunodeficiency disease with autosomal recessive inheritance. Early diagnosis and treatment will improve the outcome. The rate of autosomal recessive diseases in consanguineous families is much higher than in the general population, and primary immunodeficiency diseases do not seem to be as rare as originally thought. The high rate of consanguinity in our region (Rezaei et al., 2006) could explain the higher rate of a rare primary immunodeficiency. Genetic counseling and educational programs are essential in these regions. We recommend the general practitioners to refer any pediatric patient with striking presentation like grey hair color to pediatrician as early as possible for early supportive treatment and pre symptomatic bone marrow transplantation.

**CONFLICTS OF INTEREST**

There are no conflicts of interest.

**ACKNOWLEDGEMENTS**

We thank the patient’s family for participation and we are grateful to King Faisal Specialist Hospital staff in Riyadh for their expertise.

**REFERENCES**


Cryptosporidium parvum and its association to risk of malnutrition in school children of Northwest Mexico: A brief report

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High prevalence of malnutrition and cryptosporidiosis has been found in Mexican children, although Mexican studies on cryptosporidiosis are limited. The objective was to determine the prevalence of Cryptosporidium parvum and to establish its association with the nutritional status in school children of Northwestern Mexico. A total of 321 school children of 6 to 13 years old participated in the study. Weight-for-age, height-for-age, and body mass index for age (BMI/A) Z scores were calculated. Enzyme linked immuno-absorbent assay (ELISA) was used to detect fecal antigens of C. parvum. The overall prevalence of C. parvum was 39.3%. C. parvum-infected children were more likely to be at risk of malnutrition than C. parvum-free children. Cryptosporidiosis may be a risk factor for children malnutrition in Northwestern Mexico.

Key words: Cryptosporidium parvum, malnutrition, school children, Mexico.

INTRODUCTION

Cryptosporidiosis is a world public health problem, especially affecting immunocompromised persons, children and elderly. Twenty species of Cryptosporidium are recognized nowadays, but infection in human is attributed frequently to 8 of those species (Cryptosporidium hominis, Cryptosporidium parvum, Cryptosporidium andersoni, Cryptosporidium felis, Cryptosporidium canis, Cryptosporidium suis, Cryptosporidium muris, Cryptosporidium meleagridis) (Hadfield et al., 2011). Its transmission has been associated with contaminated drinking water and food, low socioeconomic status and overcrowding conditions (Karanis et al., 2007). This infection can be accompanied by diarrhea, abdominal pain, fever, vomiting and malabsorption in man (Chalmers and Davies, 2010) that may explain its association with low weight and height in children younger than one year in West Africa and South America (Checkley et al., 1997). C. parvum has a cosmopolitan distribution and its prevalence can range from 0.1 to 31.5% in developing countries (Karanis et al., 2007). Malnutrition is also a well-recognized worldwide health problem and many years ago it was directly responsible for 54% of deaths in children of developing countries (WHO, 2005). In 2011, the prevalences of moderate and severe underweight in preschool-children of South Asia, West and Central Africa, Sub-Saharan
Africa, and Latin America and the Caribbean were 33, 23, 21 and 3%, respectively. In addition, the prevalences of moderate and severe stunting and wasting in the same regions were 39 and 16, 39 and 12, 40 and 9, and 12 and 2%, respectively (UNICEF, 2011). In Mexico, the prevalences for stunting in preschool-children were 26.9, 21.5 and 15.5% in 1988, 1999 and 2006, respectively; and for wasting 6.2, 2.1 and 2.0%, respectively in the same years (Gonzalez-de Cossio et al., 2009). Now, it is well known that malnutrition results from different risk factors, but most of global malnutrition is associated with impaired intestinal absorptive function resulting from multiple and repeated enteric infections (Guerrant et al., 2008). This is critical in regions where children are mildly nourished even when the enteric infections are asymptomatic (Checkley et al., 1997). Mexican studies about cryptosporidiosis in children are limited. Some years ago, the only local study published a prevalence of 23% of cryptosporidiosis in 100 children (0 to 5 years) in Northwestern Mexico (Gómez et al., 1996). In 2006, cryptosporidiosis was found in 41% of 100 children under a year of age in Mexico City (Sanchez-Vega et al., 2006) and in 2010, C. parvum was found in 16% of 100 patients with diarrhea in Ciudad Juárez (Alvarado-Samarrón and Olivas-Enriquez, 2010). However, the current overall prevalence of C. parvum in the Mexican population remains unknown. On the other hand, in agreement to the National Survey in 2006, the national prevalences of low height-for-age and low weight-for-age (< -2 Z Scores) were 15.5 and 2% in children, respectively. The prevalence of low height-for-age in Northern Mexico was 8.3%, and it was around 8.0% in both the urban and rural populations of the same region (SS, 2006). However, when a child at risk of malnutrition (from -2 to < -1 Z Scores) is exposed to the cumulative effects from repetitive re-infections, the negative effects can become irreversible in the first three years of life. Based on these findings, this study investigated the prevalence of C. parvum and its association with nutritional status in school children of Northwestern Mexico.

MATERIALS AND METHODS

Study site and population

This was a cross-sectional study conducted from September to December 2008 in the state of Sonora (Northwest Mexico). Sonora is bordering to the east with the state of Chihuahua, south to the state of Sinaloa, west to the Gulf of California, and north to the US State of Arizona. Ninety-six percent of Sonora is dry and semi-dry. The average summer temperature is 38°C (June to August) and 5 to 30°C from September to January. The weather in the municipality of Hermosillo is wilderness with cool winters and can reach up to 45°C during the summer season (June, July, and August). Three primary schools in the municipality of Hermosillo were selected based on high rates of gastrointestinal infections in the local population (SS, 2008), low socioeconomic status (Alvarez et al., 2009) defined as a high percentage of parents with no school education, high number of households with no drainage, electricity, drinking water and poor quality of construction materials (INEGI, 2000) around the selected schools. A total of 720 children officially enrolled in the selected primary schools were invited to participate, while plastic containers were distributed for the collection of the stool samples (three per child). Study protocol was explained to the school authorities and parents. Three hundred and twenty one children (44.4%) agreed to participate in this study.

Ethical consideration

Individual informed consent was obtained from parents or guardians of the participating children. Of the 720 children, 352 were unwilling to participate, and 47 did not meet the study criteria (disabled, supplemented or medicated). Both participant and non-participant children were living in the same living conditions around the selected schools. The ethic committee of the Center of Research in Food and Development approved this study. Children infected with intestinal parasites received the proper treatment by the Ministry of Health.

Anthropometric measurements

Standing height was measured using a stadiometer (Holtain Ltd, Dyfed UK) with 2.05 ± 0.0005 m capacity and weight was measured to the nearest 50 g using a digital electronic scale (AND FV-150 KA1, A&D Co. LTD, Japan) using standardized recommendations. Ages were validated from reliable sources in Mexico (birth certificates and official school records). Weight-for-age, height-for-age, and body mass index for age (BMI/A) Z Scores were calculated using the software Anthro Plus (WHO, 2011). The status of malnutrition risk was defined from -2 to < -1 Z Scores from the median reference values (WHO, 2005) using the nutritional indices of height-for-age (H/A, stunting), weight-for-age (W/A), and BMI/A. The valid Z scores for analysis in this study were those considered the most occurring in our study population and they were as follows: -5.0 and +5.0 for H/A; -5.0 to +5.0 for W/A; and -4.0 to +4.0 for BMI/A (4 cases for BMI/A, 1 for H/A and 1 for W/A outside the considered range).

Fecal sample collection and fecal antigen detection by enzyme linked immuno-absorbent assay (ELISA)

Fecal samples were collected and transported to the parasitology laboratory of the Center of Research of Food and Development. Sample was weighted and 1 g homogenized and transferred into cryogenic vials (2 ml) that were properly labeled and stored at -20°C until analysis. Samples were allowed to thaw at room temperature (24°C) and 5 ml of anti-C. parvum solution was added to each vial. Content was homogenized and 200 µl of a second anti-C. parvum solution was added forming a “sandwich” with the C. parvum fecal antigen captured by the first antibody. The reaction was visualized by adding a second C. parvum antibody bound to a peroxidase conjugate with a chromogen tetrathymethylbenzidine against the second C. parvum antibody. The blue color revealed the presence of C. parvum fecal antigen bound to the anti-C parvum and reaction was stopped using phosphoric acid 1 M. A yellow color was developed and read using a Model 680 microplate reader from Bio-Rad Laboratories in an absorbance range between 450 and 650 nm. A positive and a negative standard references for quality control were included for each run. A positive result was considered when the reading was ≥ 0.150 in agreement to the manufacturer’s instructions. The DRG ELISA kit used had a sensitivity of 93% and a specificity of 98% for the diagnosis of C. parvum fecal antigens (DRG, 2010).
as the percentage of children with *C. parvum* in any of the fecal samples provided. The proportions were compared using the \( \chi^2 \) test with the corresponding odds ratios, 95% confidence intervals and \( P \) values (prevalence of infection). The association between the nutritional status and cryptosporidiosis was analyzed using multiple logistic regression models. In all models, the dependent variable was the indicator of mild or risk of malnutrition from \(-2 \) to \(-1\) \( Z \) scores for \( H/A, W/A \) and \( BMI/A \) as defined (WHO, 1996); and the \( Z \) scores of \( H/A, W/A \) and \( BMI/A \) were used to construct the stepwise models. These variables judged to be possible confounding factors such as community, age and sex (0 = female; 1 = male) were used to construct the stepwise models. Data were analyzed with the statistical software STATA/SE 12.0 (STATA 1996-2013) with a significance level of \( P \leq 0.05 \).

### RESULTS

The \( Z \) scores of 6 school children were outside of the considered data analysis interval of this study and the age of 7 school children was not confirmed. Mean age of the analyzed children (\( n = 308 \)) was 9.5 years \((\pm 1.6)\). Participation of girls (55%, \( n = 169 \)) was higher than boys (45%, \( n = 139 \)) \((z = 2.49, P = 0.013)\). Due to the low prevalence of undernutrition by \(-2 \) \( Z \) Scores for \( H/A, W/A \) and \( BMI/A \) \((3.9, 1.6 \) and \( 2.3\)% respectively), derived data from undernutrition status was not used in the multiple logistic regression models. On the contrary, the prevalence of risk of malnutrition by \( ZH/A, ZW/A \) and \( ZBMI/A \) was \( 11, 15 \) and \( 17\)% respectively. A total of 705 fecal samples were collected from September to December 2008. 20% \(( n = 62)\) and 54% \(( n = 167)\) of the children provided 2 and 3 fecal samples, respectively. The overall prevalence of *C. parvum* was 39.3% \(( n = 121)\) in this study. No difference was found in the height and \( ZBMI/A \) between the *C. parvum*-free and *C. parvum*-infected children. Although the *C. parvum*-infected children were older than the *C. parvum* free children, the latter group showed \( ZW/A \) and \( ZH/A \) higher than the *C. parvum* infected children (Table 1).

No difference was found in the prevalence of cryptosporidiosis by gender \((43\% \text{ vs. } 37\%; z = -1.48, P = 0.139)\). Univariate models (unadjusted) were constructed analyzing the risk of malnutrition with types of community, gender and age and no association was found, because community, gender and age can also influence the nutritional status (data not shown). Later, stepwise analysis was developed to test the association between the nutritional status and infection (Table 2). In this study, the children with cryptosporidiosis were 2.3 times more likely to be at risk of malnutrition by \( ZW/A \) and 2.0 times more likely to be at risk of malnutrition by \( ZBMI/A \) than the *C. parvum*-free children (Table 2). No association was found between cryptosporidiosis and risk of malnutrition by \( ZH/A \) using a similar model \((OR = 1.1, P = 0.728)\).

### DISCUSSION

This study investigated the prevalence of *C. parvum* and its association with nutritional status in 308 children (September to December 2008) of 3 public elementary schools belonging to the municipality of Hermosillo in Northwestern Mexico. In this study, the prevalence of undernutrition by \( ZH/A \) was lower \((3.9\%)\) than that \((15.5\%)\) published by the Mexican survey in 2006, although both of them showed a similar prevalence of undernutrition by \( W/A \) \((1.6\% \text{ vs. } 2\%)\). However, our study population is not representative of the children population of Northern Mexico. On the other hand, it was found that *C. parvum*-infected children showed lower means of \( ZH/A, ZW/A \) and \( ZBMI/A \) than the *C. parvum*-free children. This finding is not surprising because in 2006, another cross-sectional study in Haitian children aged 36 months old published that 49 *Cryptosporidium*-infected children showed lower \((-2)\) \( ZW/A \) and \( ZH/A \) than 41 *Cryptosporidium*-free children (Kirkpatrick et al., 2006). These authors used stool smears stained with the Ziehl-Nielsen modified acid-fast stain to look for *Cryptosporidium* species. In addition, an unexpected high prevalence of cryptosporidiosis was found in this study. This prevalence was higher than that published by only a study at local level by Gómez et al. (1996) who estimated a prevalence of cryptosporidiosis of 23.2% in 100 children using monoclonal antibodies against *C. parvum* in diarrheal stools. On the other hand, the proportion of children at risk of malnutrition was relatively high in this study. This finding is more relevant when it was found to

### Table 1. Physical characteristics of the *Cryptosporidium*-free and *Cryptosporidium*-infected school children of Northwestern Mexico.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th><em>C. parvum</em>-free (n)</th>
<th><em>C. parvum</em>-infected (n)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8.9 [1.4] (187)</td>
<td>10.3 [1.5] (121)</td>
<td>0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>36.8 (29.9 - 48.4)&lt;sup&gt;b&lt;/sup&gt; (177)</td>
<td>29.9 [24.7-39.9]&lt;sup&gt;c&lt;/sup&gt; (106)</td>
<td>0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>133.4 [10.5] (177)</td>
<td>135.9 [10.8] (106)</td>
<td>0.056&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>W/A (Z-score)</td>
<td>0.2 [1.2] (177)</td>
<td>-1.32 [9.9] (96)</td>
<td>0.044&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>H/A (Z-score)</td>
<td>-0.22 [1.1] (177)</td>
<td>-1.26 [1.1] (112)</td>
<td>0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI/A (Z-score)</td>
<td>0.53 [1.4] (178)</td>
<td>0.47 [1.5] (112)</td>
<td>0.729&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Median [25 to 75% inter-quartiles]. All other data are presented as mean ± standard deviation [SD]. <sup>b</sup>Kruskal Wallis rank sum test. <sup>c</sup>Two samples independent t-test.
be associated with cryptosporidiosis. Re-infections are serious in regions where children are at risk of malnutrition. Although the results of this study are not representative for the general population of Northwestern Mexico, this revealed that cryptosporidiosis may be a risk factor of malnutrition in school children living in our local conditions. Further studies are recommended to identify the risk factors for a better understanding of the epidemiology of C. parvum in the study sites in order to the proper authorities of Northwestern Mexico can establish strategies to prevent this infection.

ACKNOWLEDGEMENT

The authors thank the Consejo Nacional de Ciencia y Tecnología (Funds HEALTH-2009-01-113272), San Jose Hospital, the Ministry of Health of the State of Sonora, and the Centro de Investigacion en Alimentacion y Desarrollo AC for providing financial support for this study.

REFERENCES


Table 2. Unadjusted and adjusted association between the risk of malnutrition and cryptosporidiosis in school children of Northwestern Mexico.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Stepwise analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (SE)</td>
<td>95% CI</td>
</tr>
<tr>
<td>ZW/A (n=271)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. parvum-infected</td>
<td>1.7±0.50</td>
<td>1.02-3.1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.08±0.08</td>
<td>0.74-1.26</td>
</tr>
<tr>
<td>ZH/A (n=289)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. parvum-infected</td>
<td>1.1±0.32</td>
<td>0.62-1.9</td>
</tr>
<tr>
<td>ZIMC/A (n=290)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. parvum-infected</td>
<td>2.03±0.74</td>
<td>1.02-4.17</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.04±0.09</td>
<td>0.85-1.32</td>
</tr>
</tbody>
</table>

OR (SE) = odds ratio (standard error). Significance at P<0.05.
Impact of intervention on knowledge and risk factors of coronary heart disease among teachers in Sokoto, Nigeria

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Although coronary heart disease (CHD) is the most common cause of death in the developed countries, tremendous decline attributable to interventions causing reductions in population risk factors has been recorded in death rates from CHD in them in the past two decades. This study aimed to assess the impact of intervention on the knowledge and prevalence of risk factors of CHD among teachers in Sokoto. A quasi experimental study was conducted among 216 secondary school teachers selected by multistage sampling technique from April to July 2012. Anthropometric measurements, blood pressure measurement, and estimation of fasting blood sugar and cholesterol were done for the participants, together with questionnaire administration. The proportion of participants with good knowledge of CHD was low while the prevalence of the risk factors of CHD was high in both groups at baseline. At post-intervention, there was statistically significant increase in the proportion of participants with good knowledge of CHD and statistically significant reduction in the prevalence of its risk factors mainly in the intervention group. Behavioral change communication and health promotion activities to enhance smoking cessation, regular moderate exercise, healthy diet, and reduce alcohol use, should be put in place in homes and workplaces.

Key words: Coronary heart disease, risk factors, knowledge, prevalence, intervention.

INTRODUCTION

Coronary heart disease (CHD) is defined as impairment of heart function due to inadequate blood flow to it compared to its needs, caused by obstructive changes in the coronary circulation to the heart. Evidence of increased risk of CHD and other clinical manifestations of cardiovascular disease (CVD) with the presence of specific risk factors has been documented in previous epidemiological studies such as the Framingham heart study, the Standford three-community study and the multiple risk factors intervention trial (Park, 2009). CHD is one of the most common clinical manifestations of cardiovascular disease (American Heart Association (AHA), 2000). The development of CVD is promoted by major risk factors such as hypercholesterolaemia, hypertension, diabetes mellitus and smoking. These risk factors are independently associated with CVD risk and are common among adults both in the developed and developing countries. The identification of these major risk factors and the implementation of control strategies (e.g. community education and targeting of high risk factors) is essential to reduce the incidence and mortality of CHD and other cardiovascular diseases.
individuals) have contributed to the fall in CVD mortality rates observed in industrialized nations (Ford et al., 2007). The high burden of CVD in the developing countries are attributable to the increasing incidence of atherosclerotic diseases, perhaps due to urbanization and higher risk factor levels (such as obesity, diabetes mellitus, hypercholesterolaemia and hypertension), the relatively early age at which they manifest, the large sizes of the population, and the high proportion of individuals who are young adults or middle-aged in these countries (Yusuf et al., 2001).

It is estimated that the elderly population will increase globally (over 80% during the next 25 years), with a large share of this rise in the developing world, because of expanding populations. Increased longevity due to improved social and economic conditions associated with lifestyle changes in the direction of a rich diet and sedentary habits, is believed to be one of the main contributors to the incremental trend in CVD in the last century (Dominguez et al., 2006).

CHD is the most common cause of death in the developed countries, and has now become a problem of public health importance in the developing countries including Nigeria. In the UK, it caused almost one in five deaths in 2003. However, death rates from CHD in the UK have halved in the past two decades. Most of this decline (58%) has been attributed to interventions causing reductions in population risk factors (Unal et al., 2004). In most industrialized countries in which declines in mortality from CHD have been carefully examined, reductions in major risk factors have contributed to the declines at about the same level as specific medical treatments and interventions for CHD. A study by Ford et al. (2007) recently showed that, about 44% of the decline in US deaths due to CHD from 1980 through 2000 was attributable to reductions in major risk factors, and approximately 47% to evidence-based medical treatments.

Knowledge is an important pre-requisite for implementing the various preventive strategies for CHD. For behavioral change to occur, an individual must be aware of the potential negative consequences of his or her current actions. The Health-Belief-Model (HBM), suggests that a person must feel susceptible to the disease in order to change his or her behavior (Jones et al., 2006). Knowledge of the risk factors of the disease is essential for a person to make an informed decision about engaging in or continuing certain behaviors that may increase disease risk, such as smoking, not exercising or consuming high fat foods (Homko et al., 2008). It has been reported that improving cardiac related knowledge to further healthy lifestyle is the best preventive strategy against CHD (Nidal et al., 2010). In studies by Holiman et al. (2006) and Alm-Roijer et al. (2006) it was reported that, knowledge of risk factors of CHD improves adherence to advice on lifestyle changes and medication.

The prevalence of CHD in the Nigerian population is unknown, even though reports from several hospital based studies show that CHD is uncommon and does not contribute significantly to morbidity and mortality from cardiovascular diseases in Nigeria, with CHD constituting 1 in 20,000 to 1 in 13,500 medical admissions over a period of 10 to 15 years at the University College Hospital, Ibadan and the Lagos University Teaching Hospital, Lagos respectively; available evidence shows an increase in the incidence of the disease in the country over the last four decades (Nwanell, 2010).

Also, recent reports show a high prevalence of the risk factors of CHD in Nigeria. In 2008, the prevalence of hypertension in Nigeria was estimated at 42.8%, diabetes mellitus was estimated at 8.5%, obesity was estimated at 6.5%, raised cholesterol was estimated at 16.1%, current daily smoking of tobacco was estimated at 4.6%, while the cardiovascular diseases (CVDs) accounted for an estimated 12% of all deaths in Nigeria (World Health Organization (WHO), 2011).

A cross sectional survey of knowledge and prevalence of risk factors of CHD among teachers in Calabar, Nigeria reported poor knowledge and high prevalence of the risk factors of the disease (Ansah et al., 2007). The school is an institution for socialization, knowledge and health promoting behaviors acquired by teachers, in addition to preventing them from developing CHD would be passed to their students. The students being young adults are at a critical transition period in their lives, it is believed that behavior patterns and trajectories established now will influence their health for a lifetime and also that of the next generation when they grow up and become parents (Tsigos et al., 2008).

Previous studies in Nigeria primarily examined the prevalence of the risk factors of CHD; despite the high prevalence reported in several studies, there is a dearth of literature on interventions targeted at the risk factors of the disease in the country. This study aimed to assess the impact of intervention on the knowledge and prevalence of risk factors of CHD among teachers in Sokoto.

METHODOLOGY

Study design and population

The study was quasi experimental in design, with pre- and post-test design as in the model described by Fisher et al. (1991) among secondary school teachers in Sokoto metropolis, the capital of Sokoto state, in North Western Nigeria, from April to July 2012. The metropolitan city of Sokoto lies between longitude 05°11' to 13°03' East and latitude 13°00' to 13°06' North and covers an area of 60.33 km². Those eligible for the study were teachers that had worked for up to one year in the teaching profession, pregnant women and those with physical limitations that hinder or prevent exercise were excluded.

The minimum sample size was estimated at 98, and adjusted to 108 to compensate for non-response (with an anticipated 95% response rate) using the formula for comparison of proportions in independent groups (Ibrahim, 2009).
The level of significance was set at 5% (α = 0.05), and a power of 80%, where \( n = \) minimum sample size per group, \( Z_\alpha \) = two-sided percentage point of the normal distribution corresponding to the required significance level (\( α = 0.05 \) = 1.645, \( Z_β \) = one-sided percentage point of the normal distribution corresponding to 100% – the power (that is, 100% – 80% = 20% = 0.20) = 0.84, \( P \) = mean proportion of factor under study (knowledge of obesity as a risk factor for CHD = 41.6%) observed at baseline in a previous study (Ansa et al., 2007) and the projected proportion post-intervention based on the proposed hypothesis of 20% increase = (41.6% + 61.6%)/2 = 51.6% = 0.52, \( D \) = difference between the proportions = 61.6% - 41.6% = 20% = 0.20.

The eligible participants were selected by multistage sampling technique. At the first stage, out of the 4 Local Government Areas (LGAs) in the metropolis, 2 were randomly allocated by ballot into intervention group LGAs and 2 into control group LGAs. In the two intervention group LGAs, 4 of 16 schools and 2 of 7 schools were selected as study centers; while in the two control group LGAs, 5 of 18 schools and 1 of 4 schools were selected as study centers. At the second stage, selection of study participants in each of the selected secondary schools was done by systematic sampling technique using the staff list in the schools to constitute the sampling frame. Proportionate allocation (based on staff population) was applied in the selection of study participants in the selected schools.

**Data collection at pre-intervention phase**

The methods of data collection comprised of personal interview, physical and biochemical assessments. A standardized semi-structured, interviewer-administered questionnaire was used to obtain information on the socio-demographic characteristics of the study participants, awareness of CHD and its risk factors and behavioral measurements. The questions on awareness of CHD risk factors were adapted from the American Heart Association’s questionnaire that was used for a national survey on knowledge of heart disease among women (Mosca et al., 2004). The questions on behavioural measurements were adapted from the WHO STEPS Instrument for chronic diseases risk factors surveillance that was used for a national survey on health behaviour monitor among Nigerian adult population (Nigeria Heart Foundation (NHF) and Federal Ministry of Health (FMoH), 2003). The instruments were pre-tested in a pilot study among 7 bankers and 10 teachers in one of the banks and schools not selected for the study, the necessary adjustment was effected based on the observations made during the pre-test.

Weight was measured with shoes off to the nearest 0.5 kg using a Seca optimal scale; it was validated with a standard weight and corrected for zero error, the pre- and post-intervention measurements were taken by the same research assistant, to prevent inter-observers’ error.

Height was measured without shoes to the nearest 0.5 cm using a stadiometer. Blood pressure was measured using a sphygmomanometer (Dekamet MG3, England) and stethoscope (Littman quality) with all tight clothing and other similar materials removed from the arm and in the sitting position. The first measurement was taken after the participant had rested for at least 10 min in a sitting position with the arm rested on a table such that the middle of the forearm was about the level of the heart. The second measurement was taken at the end of the interview; the mean of the 2 readings was used in the analysis to prevent error due to subject variation. Also the pre-intervention and post-intervention measurements were taken by the same research assistant to prevent inter-observers’ error.

Acucheck glucometer was used for blood sugar analysis; capillary whole blood was obtained from the participants early in the morning after an overnight fast. Rayto RT-9200 semi-auto chemistry analyzer (spectrophotometer) was used for analysis of fasting serum total cholesterol.

**Intervention phase**

The components of the intervention comprised of health communication, moderate exercise schedule and dietary control. The health communication aspect was to make the participants have a clear understanding of the symptoms and signs, risk factors and prevention of CHD and the anticipated effectiveness of the proposed intervention. It consisted of a lecture session (reinforced with wall mounted information, posters and handbills), held jointly for the intervention group participants. It was held after the collection of baseline data, the lecture on CHD lasted 40 min, while 20 min was given for questions and answers. This was followed by fortnightly discussion sessions in each of the schools. The discussion sessions lasted 30 min per session, they were held during the morning break period in the schools (from 10.00 to 10.30 am). A roster of the discussion days (Mondays, Wednesdays and Fridays) was made and circulated to the participants in the six schools in the intervention group. A group leader was appointed by the participants in each of the schools to facilitate prompt and adequate communication with the participants, and also ensure effective coordination of the activities in the respective study centers. The discussion sessions enabled reinforcement of the information communicated at the lecture session and provided an avenue for feedback from the participants on compliance with the moderate scheduled exercise. Complaints were also entertained and addressed as appropriate; those with problems requiring medical attention were referred to the physicians. A telephone line (GSM) was also dedicated for communicating with the participants, especially for complaints that require immediate attention, the GSM numbers of the participants were registered with the identification numbers issued to them during registration at the stage of enrolment into the study.

Moderate scheduled exercise sessions were held 5 days in a week (Mondays to Fridays), comprising of any, or a combination of the following exercises; brisk walking, bicycling, playing football or basketball, running, jogging, swimming and playing tennis or squash. Each exercise session lasted for a minimum of 30 min but not longer than 1 h. Each participant was issued an exercise log book for keeping records of the exercise sessions observed, so as to monitor compliance (since the exercise sessions were held at convenient locations chosen by the participants themselves, in view of religious and socio-cultural factors).

A nutritionist was recruited to coordinate the dietary control aspect of the study, dietary patterns were recommended for the participants (Graaffnigo et al., 2006). They were instructed to reduce their calorie intake by reducing the serving size of their meal by between a quarter to half, avoid snacks and fruit juice, and also to desist from taking heavy meals late at night. They were also instructed to replace high calorie foods with vegetables, fruits, whole grains and legumes. Demonstrations were held (during the discussion sessions) on how to measure the serving sizes of the common locally available food items, planning of meals and the appropriate food serving sizes to achieve reduction in calorie intake of about 500 to 1,000 kcal/day less than the usual intake. A weight loss of 1 to 2 pounds (0.45 to 0.91 kg) per week was anticipated.

**Data collection at post-intervention phase**

Data was collected again at post-intervention (in the intervention
group) and at the end of the study (in the control group). This was done after the completion of the 3 months period of scheduled exercise (5 times in a week), and fortnightly group discussion sessions in the intervention group. The same instruments of data collection used at baseline were used. After the post-intervention data collection, the same intervention offered to the intervention group was also offered to the control group for the benefit of the participants.

Three medical officers, two nurses and three laboratory scientists assisted in data collection after pre-training on the objectives, selection of participants and use of survey instruments. Ethical permission to carry out the study was obtained from the Ethical committee of the Usman Danfodiyo University Teaching Hospital Sokoto. Permission to carry out the study in the schools was sought and obtained from Sokoto State Ministry of Education and Ministry of Science and Technology. Informed written consent was obtained from the participants before data collection.

Operational definition of terms

Body mass index (BMI) was calculated as weight (kg) divided by height$^2$ (m$^2$) and was used as marker for overweight and obesity (Tsigos et al., 2008). Underweight was defined as BMI less than 18.5 kg/m$^2$, normal weight was defined as BMI of 18.5 to 24.9 kg/m$^2$, overweight was defined as BMI of 25.0 to 29.9 kg/m$^2$, while obesity was defined as BMI of 30.0 kg/m$^2$ and above. Diabetes mellitus was defined using the World Health Organization criteria (WHO, 1999) as fasting plasma whole glucose ≥6.1 mmol/l (110 mg/dl). Hypercholesterolaemia was defined using the American Heart Association criteria (AHA, 2002) as fasting serum total cholesterol (Tc) ≥5.2 mmol/l (200 mg/dl). Hypertension was defined using the World Health Organization and International Society of Hypertension criteria (WHO and ISH, 2003) as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg or both or self reported antihypertensive medication during the past 1 week.

Data analysis

Data collation and sorting was done manually. Computer data processing was done using the Statistical Package for Social Sciences (SPSS) version 17 computer statistical software package. Frequency runs were done for further editing and cleansing of the e-data. Frequency distribution tables were constructed; cross tabulations were done to examine relationship between categorical variables. Knowledge of symptoms and signs of CHD was scored on a 9 item scale, while 7 item scales were used for scoring knowledge of risk factors and prevention of CHD. Correct response was scored one and incorrect response or none- response was scored zero. Respondent scoring less than 50% was considered to have poor knowledge while scores of 50% and above were graded as having good knowledge. The independent student’s t-test was used for comparison of mean differences between the two groups at pre-intervention. Comparison of the post-intervention data in the two groups was done in order to demonstrate the effect of the intervention program. The Chi-square test was used to compare differences between proportions while the paired student’s t-test was used for comparison of mean differences. All statistical analysis was set at 5% level of significance (that is, p ≤ 0.05).

RESULTS

A total of 216 participants, comprising of 108 participants in the intervention group and 108 participants in the control group, participated in the study at the pre-intervention stage. At the post-intervention stage of data collection, there were 200 participants, comprising of 101 participants in the intervention group and 99 participants in the control group; thus giving an attrition rate of 6.5 and 8.3% for the intervention group and control group, respectively. Most of the participants in both the intervention group (38.0%) and control group (39.8%) were in the 30 to 39 years age group. Majority of the participants in both the intervention group (58.3%), and control group (60.2%), were males. Islam was the predominant religion among the participants in both groups; 63.0 and 69.4% of the participants in the intervention and control groups, respectively, were Muslims. Majority of the participants in both the intervention group (68.5%) and control group (67.6%), had university education, only a few of the participants in both groups graduated from either the college of education or polytechnic. There was no statistically significant difference between the two groups in any of the socio-demographic variables as shown in Table 1.

Impact of intervention on participants’ knowledge of symptoms and signs of CHD

The impact of intervention on the knowledge of the symptoms and signs of CHD that was assessed at pre-intervention is shown in Table 2. The proportion of participants with good knowledge of the signs and symptoms of CHD increased tremendously among the intervention group participants from 34 (31.5%) of the 108 participants at the pre-intervention stage to 81 (80.2%) of the 101 participants at the post-intervention stage and the difference was statistically significant ($\chi^2 = 50.052, p < 0.001$). Among the control group participants, there was a slight increase in the proportion of participants with good knowledge of the symptoms and signs of CHD from 28 (25.9%) of the 108 participants at the beginning of study to 28 (28.3%) of the 99 participants at the end of study, but the difference was not statistically significant ($\chi^2 = 0.145, p = 0.703$). Whereas, there was tremendous and statistically significant ($p < 0.001$) increase in the proportion of participants that knew the various symptoms and signs of CHD at the post-intervention stage compared to the pre-intervention stage among the intervention group participants, no statistically significant increase in knowledge of any of the symptoms and signs of CHD was observed at the end of study compared to the beginning of study among the control group participants ($p$ values ranged from 0.596 to 0.994).

Impact of intervention on participants’ knowledge of risk factors of CHD

Among the intervention group participants an appreciable and statistically significant increase was recorded in both the proportion of participants with good knowledge of the risk factors of CHD from 49 (45.4%) of the 108 participants...
Table 1. Socio-demographic profile of participants.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention group [N=108 (%)]</th>
<th>Control group [N=108 (%)]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age groups (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 - 29</td>
<td>36 (33.3)</td>
<td>35 (32.4)</td>
<td></td>
</tr>
<tr>
<td>30 - 39</td>
<td>41 (38.0)</td>
<td>43 (39.8)</td>
<td>$\chi^2 = 0.215$</td>
</tr>
<tr>
<td>40 - 49</td>
<td>24 (22.2)</td>
<td>22 (20.4)</td>
<td>p = 0.975</td>
</tr>
<tr>
<td>50 - 59</td>
<td>7 (6.5)</td>
<td>8 (7.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>63 (58.3)</td>
<td>65 (60.2)</td>
<td>$\chi^2 = 0.077$</td>
</tr>
<tr>
<td>Female</td>
<td>45 (41.7)</td>
<td>43 (39.8)</td>
<td>p = 0.445</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>32 (29.6)</td>
<td>44 (40.7)</td>
<td>$\chi^2 = 2.923$</td>
</tr>
<tr>
<td>Married</td>
<td>76 (70.4)</td>
<td>64 (59.3)</td>
<td>p = 0.058</td>
</tr>
<tr>
<td><strong>Religion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Islam</td>
<td>68 (63.0)</td>
<td>75 (69.4)</td>
<td>$\chi^2 = 1.014$</td>
</tr>
<tr>
<td>Christianity</td>
<td>40 (37.0)</td>
<td>33 (30.6)</td>
<td>p = 0.194</td>
</tr>
<tr>
<td><strong>Educational status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>College of education</td>
<td>17 (15.7)</td>
<td>21 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Polytechnic</td>
<td>17 (15.7)</td>
<td>14 (13.0)</td>
<td>$\chi^2 = 0.718$</td>
</tr>
<tr>
<td>University</td>
<td>74 (68.5)</td>
<td>73 (67.6)</td>
<td>p = 0.698</td>
</tr>
</tbody>
</table>

Table 2. Impact of intervention on participants’ knowledge of symptoms and signs of CHD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Knowledge grading</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good knowledge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-intervention [N=108 (%)]</td>
<td>34 (31.5)</td>
<td>28 (25.9)</td>
<td></td>
</tr>
<tr>
<td>Post-intervention [N=101 (%)]</td>
<td>81 (80.2)*</td>
<td>80 (74.1)</td>
<td></td>
</tr>
<tr>
<td>Beginning of study [N=108 (%)]</td>
<td>28 (25.9)</td>
<td>33 (33.3)</td>
<td></td>
</tr>
<tr>
<td>End of study [N=99 (%)]</td>
<td>28 (28.3)</td>
<td>33 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Poor knowledge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-intervention [N=108 (%)]</td>
<td>74 (68.5)</td>
<td>71 (71.7)</td>
<td></td>
</tr>
<tr>
<td>Post-intervention [N=101 (%)]</td>
<td>20 (19.8)</td>
<td>62 (62.6)</td>
<td></td>
</tr>
<tr>
<td>Beginning of study [N=108 (%)]</td>
<td>28 (25.9)</td>
<td>62 (62.6)</td>
<td></td>
</tr>
<tr>
<td>End of study [N=99 (%)]</td>
<td>28 (28.3)</td>
<td>62 (62.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms and signs of CHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain after doing some work but goes after rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (30.6)</td>
<td>30 (27.8)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7 (6.5)</td>
<td>8 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td>68 (63.0)</td>
<td>70 (64.8)</td>
<td></td>
</tr>
<tr>
<td>Beginning of study [N=108 (%)]</td>
<td>30 (27.8)</td>
<td>7 (7.1)</td>
<td></td>
</tr>
<tr>
<td>End of study [N=99 (%)]</td>
<td>28 (28.3)</td>
<td>64 (64.6)</td>
<td></td>
</tr>
<tr>
<td>Chest pain that radiates to neck, shoulder and arm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28 (25.9)</td>
<td>31 (28.7)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7 (6.5)</td>
<td>5 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td>73 (67.6)</td>
<td>72 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Beginning of study [N=108 (%)]</td>
<td>28 (25.9)</td>
<td>4 (4.0)</td>
<td></td>
</tr>
<tr>
<td>End of study [N=99 (%)]</td>
<td>33 (33.3)</td>
<td>62 (62.6)</td>
<td></td>
</tr>
<tr>
<td>Chest tightness or shortness of breath after doing some work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40 (37.0)</td>
<td>34 (31.5)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9 (8.3)</td>
<td>10 (9.3)</td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td>59 (54.6)</td>
<td>64 (59.3)</td>
<td></td>
</tr>
<tr>
<td>Beginning of study [N=108 (%)]</td>
<td>40 (37.0)</td>
<td>7 (7.1)</td>
<td></td>
</tr>
<tr>
<td>End of study [N=99 (%)]</td>
<td>33 (33.3)</td>
<td>59 (59.6)</td>
<td></td>
</tr>
<tr>
<td>Feeling of tiredness quickly, after a little work or even without doing any work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (27.8)</td>
<td>28 (25.9)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>12 (11.1)</td>
<td>9 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td>66 (61.1)</td>
<td>71 (65.7)</td>
<td></td>
</tr>
<tr>
<td>Beginning of study [N=108 (%)]</td>
<td>30 (27.8)</td>
<td>5 (5.1)</td>
<td></td>
</tr>
<tr>
<td>End of study [N=99 (%)]</td>
<td>29 (29.3)</td>
<td>65 (65.7)</td>
<td></td>
</tr>
<tr>
<td>Sudden death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>44 (40.7)</td>
<td>35 (32.4)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4 (3.7)</td>
<td>7 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td>60 (55.6)</td>
<td>66 (61.1)</td>
<td></td>
</tr>
<tr>
<td>Beginning of study [N=108 (%)]</td>
<td>44 (40.7)</td>
<td>4 (4.0)</td>
<td></td>
</tr>
<tr>
<td>End of study [N=99 (%)]</td>
<td>36 (36.4)</td>
<td>59 (59.6)</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant (p < 0.05)
Impact of intervention on participants' knowledge of CHD prevention

The impact of intervention on the knowledge of CHD prevention that was assessed at pre-intervention is shown in Table 4. A statistically significant increase ($\chi^2 = 44.053, p < 0.001$) was observed in both the proportion of participants with good knowledge of prevention of CHD among the intervention group participants from 51 (47.2%) of the 108 participants at the pre-intervention stage to 91 (90.1%) of the 101 participants at the post-intervention stage, and the proportion of participants that knew the ways of preventing the risk factors of CHD ($p < 0.001$).

Among the control group participants, although there

was statistically significant increase (p values range from 0.002 to 0.008) in the proportion of participants that knew ensuring appropriate treatment for hypertension and diabetes mellitus as ways of preventing CHD from 43 (39.8%) to 60 (60.6%) and 48 (44.4%) to 65 (65.7%), respectively, the marginal increase observed in the proportion of participants with good knowledge of CHD prevention from 46 (42.6%) of the 108 participants at the beginning of study to 48 (48.5%) of the 99 participants at the end of study was not statistically significant ($\chi^2 = 0.723, p = 0.395$).

### Impact of intervention on the prevalence of hypertension, diabetes mellitus and hypercholesterolaemia among participants

Among the intervention group participants, a statistically significant decrease in the systolic blood pressure at the post-intervention stage compared to the pre-intervention stage was recorded (Mean decrease = 2.87 mmHg, standard deviation (SD) = 9.20; $t = 3.136, p = 0.002$. The decrease recorded in the diastolic blood pressure was also statistically significant (Mean decrease = 1.49 mmHg, SD = 5.90); $t = 2.531, p = 0.013$. Among the control group participants, there was no statistically significant reduction at the end of the study compared to the beginning of the study in the systolic blood pressure (Mean decrease = 0.30 mmHg, SD = 2.24); $t = 1.347, p = 0.181$. Similarly, the decrease recorded in the diastolic blood pressure was not statistically significant (Mean decrease = 0.26 mmHg, SD = 1.50); $t = 1.747, p = 0.084$. A statistically significant decrease in the prevalence of hypertension was recorded at the post-intervention stage compared to the pre-intervention stage among the intervention group participants from 29.6 to 17.8% ($\chi^2 =$
Table 5. Impact of intervention on the prevalence of hypertension, diabetes mellitus and hypercholesterolaemia among participants.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measure</th>
<th>Intervention group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>Mean systolic BP</td>
<td>115.84 ± 18.73</td>
<td>112.97 ± 16.74</td>
</tr>
<tr>
<td></td>
<td>Decrease in mean systolic BP</td>
<td>2.87 ± 9.20*</td>
<td>0.30 ± 2.24</td>
</tr>
<tr>
<td>Diastolic BP (DBP)</td>
<td>Mean diastolic BP</td>
<td>78.02 ± 11.54</td>
<td>76.54 ± 9.72</td>
</tr>
<tr>
<td></td>
<td>Decrease in mean diastolic BP</td>
<td>1.49 ± 5.90*</td>
<td>0.26 ± 1.50</td>
</tr>
<tr>
<td>BP status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal BP</td>
<td></td>
<td>76 (70.4)</td>
<td>83 (82.2)</td>
</tr>
<tr>
<td>Hypertensive</td>
<td></td>
<td>32 (29.6)</td>
<td>18 (17.8)*</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dl)</td>
<td>Mean fasting blood sugar</td>
<td>85.13 ± 43.71</td>
<td>78.44 ± 18.67</td>
</tr>
<tr>
<td></td>
<td>Decrease in mean fasting blood</td>
<td>6.69 ± 10.38*</td>
<td>1.80 ± 9.10</td>
</tr>
<tr>
<td></td>
<td>sugar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sugar status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td>97 (89.8)</td>
<td>98 (97.0)</td>
</tr>
<tr>
<td>Diabetic</td>
<td></td>
<td>11 (10.2)</td>
<td>3 (3.0)*</td>
</tr>
<tr>
<td>Fasting blood cholesterol</td>
<td>Mean fasting blood cholesterol</td>
<td>185.23 ± 31.68</td>
<td>172.52 ± 24.92</td>
</tr>
<tr>
<td></td>
<td>Decrease in mean fasting blood</td>
<td>12.71 ± 19.54*</td>
<td>5.17 ± 13.42*</td>
</tr>
<tr>
<td></td>
<td>cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood cholesterol status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td>11 (10.2)</td>
<td>32 (31.7)</td>
</tr>
<tr>
<td>Borderline high</td>
<td></td>
<td>65 (60.2)</td>
<td>55 (54.5)</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td>32 (29.6)</td>
<td>14 (13.9)*</td>
</tr>
</tbody>
</table>

*Statistically significant (p < 0.05).

3.998, p = 0.046). The decrease recorded in the prevalence of hypertension at the end of study compared to the beginning of study among the control group participants from 22.2 to 19.2% was not statistically significant ($\chi^2 = 0.288, p = 0.591$).

A statistically significant reduction in the fasting blood sugar was recorded among the intervention group participants (Mean decrease = 6.69 mg/dl, SD = 10.38); $t = 6.530, p < 0.001$. There was also a statistically significant decrease in the prevalence of diabetes mellitus among them from 10.2% at pre-intervention to 3.0% at post-intervention ($\chi^2 = 4.347, p = 0.037$). The decrease recorded in the fasting blood sugar level of the control group participants at the end of study compared to the beginning of study was not statistically significant (Mean decrease = 1.80 mg/dl, SD = 9.10); $t = 1.967, p = 0.052$. The decrease recorded in the prevalence of diabetes mellitus among the control group participants from 12.0% at the beginning of study to 7.1% at the end...
Table 6. Impact of intervention on participants’ lifestyle and prevalence of overweight and obesity.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Response/Measure</th>
<th>Intervention group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-intervention</td>
<td>Post-intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[N= 108 (%)]</td>
<td>[N= 101 (%)]</td>
</tr>
<tr>
<td>Engage in moderate leisure exercise</td>
<td>Yes</td>
<td>49 (45.4)</td>
<td>90 (89.1)*</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>59 (54.6)</td>
<td>11 (10.9)</td>
</tr>
<tr>
<td>Physical activity status</td>
<td>Active</td>
<td>85 (78.7)</td>
<td>94 (93.1)</td>
</tr>
<tr>
<td></td>
<td>Inactive</td>
<td>23 (21.3)</td>
<td>7 (6.9)*</td>
</tr>
<tr>
<td>Currently smoke cigarette</td>
<td>Yes</td>
<td>4 (3.7)</td>
<td>3 (3.0)*</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>104 (96.3)</td>
<td>98 (97.0)</td>
</tr>
<tr>
<td>Eat fatty foods</td>
<td>Yes</td>
<td>74 (68.5)</td>
<td>32 (31.7)*</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>34 (31.5)</td>
<td>68 (68.3)</td>
</tr>
<tr>
<td>Drank alcohol in the past 30 days</td>
<td>Yes</td>
<td>11 (10.2)</td>
<td>3 (3.0)*</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>97 (89.8)</td>
<td>98 (97.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean weight</td>
<td>68.65 ± 17.62</td>
<td>67.64 ± 16.55</td>
</tr>
<tr>
<td></td>
<td>Decrease in mean weight</td>
<td>1.01 ± 2.61*</td>
<td>nil</td>
</tr>
<tr>
<td></td>
<td>Increase in mean weight</td>
<td>nil</td>
<td>67.64 ± 16.55</td>
</tr>
<tr>
<td>Weight category</td>
<td>Underweight/normal weight</td>
<td>-</td>
<td>63 (58.3)</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>-</td>
<td>31 (28.7)</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>-</td>
<td>14 (13.0)</td>
</tr>
</tbody>
</table>

*Statistically significant (p < 0.05).

end of study was also not statistically significant ($\chi^2 = 0.236, p = 1.404$).

Among the intervention group participants, a statistically significant decrease in the fasting blood cholesterol at the post-intervention stage compared to the pre-intervention stage was recorded (Mean decrease = 12.71 mg/dl, $SD = 19.54$); $t = 6.540, p < 0.001$. A statistically significant decrease in the prevalence of hypercholesterolaemia was recorded from 29.6% at pre-intervention to 13.9% at post-intervention ($\chi^2 = 17.818, p < 0.001$). Among the control group participants, a statistically significant decrease at the end of study compared to the beginning of study in the fasting blood cholesterol level was also recorded (Mean decrease = 5.17 mg/dl, $SD = 13.42$); $t = 3.834, p < 0.001$. The decrease recorded in the prevalence of hypercholesterolaemia from 31.5% at the beginning of study to 24.7% at the end of study was not statistically significant ($\chi^2 = 2.748, p = 0.253$) as shown in Table 5.

Impact of intervention on participants’ lifestyle and prevalence of overweight and obesity

The impact of intervention on participants’ lifestyle and the prevalence of overweight and obesity at post-intervention compared to pre-intervention is shown in Table 6. The proportion of participants that routinely engage in moderate leisure exercise increased among the intervention group participants from 49 (45.4%) of the 108 participants at the pre-intervention stage, to 90 (89.1%) of the 101 participants at the post-intervention stage, and the increase was found to be statistically significant ($\chi^2 = 44.824, p < 0.001$). There was a statistically significant decrease in the proportion of participants that do not routinely engage in any form of physical activity (sedentary lifestyle) from 23 (21.3%) of the 108 participants at pre-intervention to 7 (6.9%) of the 101 participants at post-intervention ($\chi^2 = 8.761, p = 0.003$). Among the control group participants, the slight increase that was observed in the proportion of participants that do not routinely engage in any form of physical activity (sedentary lifestyle) from 8 (7.4%) of the 108 participants at intervention to 2 (2.0%) of the 99 participants at the end of study, was not statistically significant ($\chi^2 = 2.096, p = 0.148$). The decrease that was recorded in the proportion of participants that do not routinely engage in any form of physical activity from 8 (7.4%) of the 108 participants at the beginning of study to 2 (2.0%) of the 99 participants at
the end of study was also not statistically significant ($\chi^2 = 3.261, p = 0.071$).

The proportion of participants that currently smoke cigarette decreased from 4 (3.7%) of the 108 participants at pre-intervention to 3 (3.0%) of the 101 participants at post-intervention, among the intervention group participants, but the difference was not statistically significant ($\chi^2 = 0.087, p = 0.768$). Similarly, the decrease recorded in the proportion of participants that currently smoke cigarette among the control group participants from 6 (5.6%) of the 108 participants at the beginning of study to 5 (5.1%) of the 99 participants at the end of study was not statistically significant ($\chi^2 = 0.026, p = 0.871$).

Among the intervention group participants, there was a statistically significant decrease in the proportion of participants that eat fatty foods from 74 (68.5%) of the 108 participants at pre-intervention to 32 (31.7%) of the 101 participants at post-intervention ($\chi^2 = 28.332, p < 0.001$). Among the control group participants, the slight decrease in the proportion of participants that eat fatty foods from 78 (72.2%) of the 108 participants at the beginning of study to 70 (70.7%) of the 99 participants at the end of study was not statistically significant ($\chi^2 = 0.050, p = 0.808$).

Among the intervention group participants, there was a statistically significant decrease in the proportion of participants that drank alcohol in the past 30 days, from 11 (10.2%) of the 108 participants at pre-intervention to 3 (3.0%) of the 101 participants at post-intervention ($\chi^2 = 4.347, p = 0.037$). Among the control group participants, the decrease in the proportion of participants that drank alcohol in the past 30 days, from 11 (10.2%) of the 108 participants at the beginning of study to 8 (8.1%) of the 99 participants at the end of study was not statistically significant ($\chi^2 = 0.274, p = 0.600$).

The intervention group participants recorded a statistically significant reduction in mean weight from 68.65 kg at the pre-intervention stage to 67.64 kg at the post-intervention stage ($t = 3.895, p < 0.001$). The proportion of participants with overweight remained constant at 28.7% both at pre-intervention and post-intervention, while the proportion of obese participants decreased from 14 (13.0%) of the 108 participants at pre-intervention to 11 (10.9%) of the 101 participants at post-intervention; but the difference was not statistically significant ($\chi^2 = 0.225, p = 0.894$). Among the control group participants, no reduction in mean weight was recorded, the mean weight increased from 72.73 kg at the beginning of study to 73.33 kg at the end of study, but the increase was not statistically significant (Mean weight increase = 0.61 kg, SD = 3.08); $t = 1.965, p = 0.053$. The proportion of participants with overweight decreased from 21 (19.4%) of the 108 participants at the beginning of study, to 18 (18.4%) of the 99 participants at the end of study, while the proportion of obese participants increased marginally from 27 (25.0%) of the 108 participants at the beginning of study to 25 (25.5%) of the 99 participants at the end of study, and the difference recorded was not statistically significant ($\chi^2 = 0.040, p = 0.980$).

Among the female participants in the intervention group, a slight decrease was recorded in the proportion of participants that reported use of oral contraceptives in the past 1 month from 6 (13.3%) of the 45 participants at pre-intervention to 5 (12.5%) of the 40 participants at post-intervention. The decrease recorded was not statistically significant ($\chi^2 = 0.013, p = 0.909$).

A marginal increase was recorded in the proportion of participants that reported use of oral contraceptives in the past 1 month among the female participants in the control group, from 4 (9.3%) of the 43 participants at the beginning of study to 4 (9.5%) of the 42 participants at the end of study. The increase was also not statistically significant ($\chi^2 = 0.001, p = 0.972$).

**DISCUSSION**

The intervention group participants recorded statistically significant increase in the proportion of participants with good knowledge of symptoms and signs, risk factors and prevention of CHD at post-intervention compared to pre-intervention; but such a uniform pattern was not observed among the control group participants. Whereas, there was statistically significant ($p < 0.001$) increase in the proportion of participants that knew the various symptoms and signs, risk factors and prevention of CHD at post-intervention compared to pre-intervention, among the intervention group participants, such a uniform pattern was not observed among the control group participants. However, a statistically significant increase in the proportion of participants that knew diabetes mellitus ($p < 0.001$) and hypertension ($p = 0.005$) as risk factors of CHD was recorded at the end of study compared to the beginning of study among the control group participants. A statistically significant increase was also recorded in the proportion of participants that knew appropriate treatment of diabetes ($p = 0.002$) and hypertension ($p = 0.008$) as prevention for CHD at the end of study compared to the beginning of study among the control group participants. This could be due to the fact that the study being a screening test, generated awareness about the disease among the control group participants. In addition, participants with abnormal test results among the control group, particularly those that were referred to physicians for treatment, probably obtained information about the risk factors and prevention of the disease from the hospital and other sources, considering the fact that an abnormal test result could have influenced their perception of vulnerability to the disease. The findings in this study are in concordance with the findings in a study by Huang et al. (2002) that reported improvement in health promotion knowledge and behaviors following a health promotion education program among the elderly in the community, and another study by Kirk-Kirk-Gardner and...
Steven, (2003) that reported improved knowledge and reduced risk behaviors in a community based program on heart health promotion among healthy adults over a period of 3 months, it has also revealed that education programs are effective in improving health promotion knowledge and behaviors.

The statistically significant increases recorded in the proportion of participants with good knowledge of hypertension and diabetes mellitus in both the intervention and control groups in this study unequivocally demonstrates the potential of a screening interventional program like this in generating awareness about these diseases in the general population. This is of immense public health significance as it elucidates the implications of the non-inclusion of screening for hypertension and diabetes mellitus in the periodic Nigeria Demographic and Health Surveys (NDHS), despite the high prevalence of the diseases in the country (National Population Commission (NPC) and ICF Macro, 2009).

The statistically significant decrease that was recorded in the prevalence of hypertension among the intervention group participants from 29.6% at pre-intervention down to 17.8% at post-intervention (p = 0.046) was probably due to the medications the participants with hypertension that were referred to the physicians received and improved compliance with their medications following the health communication aspect of the intervention. The findings in this study are similar to those in a study by Steven et al. (2001) that reported significant reductions in blood pressure after multifaceted physical activity interventions among men and women aged 30 to 54 years in 6 months.

Similarly, a statistically significant decrease (p = 0.037) was observed in the prevalence of diabetes mellitus at the post-intervention stage compared to the pre-intervention stage among the intervention group participants in contrast to the control group participants. This is in concordance with the findings in a study by Castaneda et al. (2002) that reported reduced plasma glycosylated hemoglobin, increased muscle glycogen and reduction in the dose of prescribed diabetic medications among intervention group participants in a randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. Interventions incorporating physical activity, diet, or a combination of both have been documented to reduce progression to diabetes and reverse existing diabetes (Greaves et al., 2011).

A statistically significant decrease (p < 0.001) was also observed in the prevalence of hypercholesterolemia at the post-intervention stage compared to the pre-intervention stage among the intervention group participants in contrast to the control group participants. Similar to the findings in this study, Metz et al. (2000) also reported significant decreases in total cholesterol and triglycerides levels with diet interventions among persons with hypertension and dyslipidaemia.

A statistically significant reduction (p values range from < 0.001 to 0.037) in CHD related lifestyles such as physical inactivity, alcohol ingestion and consumption of fatty foods was recorded among the intervention group participants in contrast to the control group participants in this study. The slight decrease recorded in the proportion of participants that currently smoke cigarette, and the female participants that reported use of oral contraceptives in the past 1 month at the post-intervention stage compared to the pre-intervention stage, in both groups, could be due to the low prevalence of these CHD related lifestyles among them. The behavioral change observed among the intervention group participants compared to the control group participants in this study, supports the submissions of previous studies (Bayne-Smith et al., 2004; Eshar et al., 2010; Homko et al., 2006) on the significance of knowledge of modifiable risk factors of CHD as a key component of behavioral change decision making, in addition to providing cues for action.

A statistically significant (p < 0.001) reduction in mean weight was recorded among the intervention group participants, at the post-intervention stage compared to the pre-intervention stage, with a mean weight reduction of 1.0 kg in 3 months. No weight reduction was recorded among the control group participants, but the slight increase in mean weight (mean weight gain of 0.6 kg) that was recorded at the end of study compared to the beginning of study among the control group participants was not statistically significant (p = 0.053). The findings in this study agree with the findings in a primary care intervention program among obese adults with CHD risk factors by Read et al. (2004) that reported a statistically significant mean weight reduction of 3.1 kg over the same period of 3 months. The higher mean weight reduction recorded in the study among the obese adults could be due to the fact that the exercise sessions were held jointly in the health facilities, thus making ascertainment of compliance more feasible; in contrast to the situation in this study whereby the participants observed the exercise sessions individually at home due to the challenges posed by religious and socio-cultural factors. This highlights the need for further research in developing intervention programs compatible with religious and socio-cultural background across Nigeria.

**Conclusion**

Poor baseline knowledge of CHD and high prevalence of its risk factors among teachers in Sokoto was demonstrated in this study. Intervention made significant impact in improving knowledge of CHD and reducing the prevalence of its risk factors among the intervention group participants. Behavioral change communication and health promotion activities to enhance smoking cessation, regular moderate exercise, healthy diet, and reduce alcohol use, should be put in place in homes and workplaces.
LIMITATIONS TO THE STUDY

The study involved collection of blood samples for biochemical analysis and measurement of blood pressure and anthropometry, it was therefore more of a multi-phasic screening test. The results were communicated to the participants as demanded by them, and those with abnormal results that require treatment were referred to the physicians. Those with abnormal test results (especially those that were referred to the physicians) among the control group participants could seek for information about the disease from the healthcare providers and other sources. Those that were referred to the physicians could receive counseling on CHD related behavioral modifications in the course of their treatment. These could distort the pattern of knowledge, CHD related risk behavior, and prevalence of CHD risk factors among the control group participants. The exercise sessions were observed individually at home due to the challenges posed by religious and socio-cultural factors, ascertainment of compliance was therefore difficult.

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Psycho-immunological rehabilitation of advanced cancer patients with psychogenic medical history

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The aim of this work is approbation of the pathogenetically substantiated psycho-immunological rehabilitation of advanced cancer patients with psychogenic medical history. 17 advanced cancer patients (with 6 various types of cancer) took part in this study. All psycho-emotional disorders were diagnosed clinically and psychometrically (SCL 90). The treatment of signs and symptoms of mentioned disorders included hypnotherapy and psychotropic drugs. The specific anti-tumor activity of the immune system was assessed by the delayed type hypersensitivity skin reaction on the tumor-associated antigens. An activation of specific anti-tumor immunity was provided only after stable clinical effect of psycho-correction by specially developed methods of epicutaneous and modified extra-corporeal activation. The effective treatment of psycho-emotional disorders had a direct correlation with spontaneous increase in specific anti-tumor activity of the immune system (p < 0.0008). The catamnesis showed that only 5 advanced cancer patients, who were provided with whole course of psycho-immunological rehabilitation survived for 1.5 years and up to 7 years after psycho-immunological rehabilitation. The rest 12 patients died. This study showed some clinical opportunities of positive influence of special psycho-immunological rehabilitation on to the course of a disease of advanced cancer patients with psychogenic medical history.

Key words: Advanced cancer, anti-tumor immunity, cancer rehabilitation, psycho-emotional disorders, psychogenic medical history.

INTRODUCTION

Advanced cancer is the malignant disease that has spread to other places in the body and usually cannot be cured or controlled with treatment. Treatment and care of advanced cancer patients are focused on the management and relief of symptoms, improving the patient's comfort and quality of life. Actually, such patients are given symptomatic treatment. At the same time, the status of anti-tumor immunity is being a key link in the carcinogenesis chain of advanced cancer. That means the anti-tumor immunity could be considered as the target for pathogenetically justified immunorehabilitation treatment. It is also known that the activity of anti-tumor immunity determines survival of patients with cancer. It should be mentioned that an active development of immunotherapy as the mean of immunorehabilitation of compromised immunity of patients living with cancer had promised drastic changes in the management of cancer as well as an increase in survival of patients living with cancer. However, these expectations have not been fulfilled so far. Clinical studies show that initially compromised anti-tumor immunity of patients living with cancer cannot be surely recovered by means of immunorehabilitation. At the same time, usage of immunotherapy of some patients could not only be useless, but dangerous due to possibility of stimulation of cancer development for example through induction Treg cells (Curiel, 2007).
At first sight, an idea of administering pathogenically justified immunorehabilitation to the patients with advanced cancer seems to be inappropriate and even absurd. It could be accepted if to look on the immunorehabilitation from deterministic positions of cell/molecular and/or genetic levels.

The systemic view of holistic approach suggests mandatory taking into consideration the state of higher nervous activity (mental state), which provides serious influence on development and outcome of cancer disease. For instance, depression is alarming the potentially short life of patients living with cancer (Onitilo et al., 2006). In this regard, we assumed that some patients with advanced cancer suffer from psychogenically determined immunosuppression as an outcome of untreated psycho-emotional disorders which have occurred before diagnosis of cancer. Actually, those patients went through massive psycho-traumatic events which were added up by massive stress connected with first time diagnosis of cancer. We also assumed that immunorehabilitation of advanced cancer patients with a psychogenic medical history should be preceded with effective correction of psycho-emotional disorders in order to avoid psychogenic immunosuppressive influence. The objective of this work is development and implementation of psycho-immunological rehabilitation of advanced cancer patients with psychogenic medical history.

Theoretical justification for psycho-immunological rehabilitation of advanced cancer patients with psychogenic medical history

Nowadays, there is no doubt that the immune dysfunctions are the backbone of the tumor pathogenesis. This immune dysfunctions at the same time with destruction of the cellular genetic apparatus in the malignant cells appeared in the form of the cell component of the immune system dysfunction along with malfunction of cell control and cell differentiation mechanisms, immune tolerance and inability to provide effective immune response to developing tumor (Finn, 2008; Prendergast, 2008). In this connection, it was logical to use the wide range of immunotherapy methods in modern oncology. Despite that it was a new step in malignant tumor treatment, it has not solved the problem of its effective treatment (Nedospasov and Kuprash, 2007; Harada and Yonemitsu, 2011). At the same time, laboratory and clinical trials have proved tied and multifunctional interconnections between two most important integrative systems of the human organism which are the immune and the nervous systems (Hall et al., 1985; Pert et al., 1985; Ader and Cohen, 1985), that formed the base for development of modern scientific trends which are the psychoneuroimmunology and psycho-immunology of cancer (O’Sullivan et al., 1994).

The conclusions of the scientific research on influence of chronic psycho-emotional stress (CPES) to an organism of healthy and unhealthy individuals, including those with cancer are most interesting from the practical approach point of view. Nowadays, the somatic outcomes of CPES are well known. So the CPES is able to damage the cell’s DNA and inhibit DNA reparation by activation of endogenous mutagens, which are the reactive species of oxygen and nitrogen that forms genome instability (Dimitroglou et al., 2003; Gidron et al., 2006). CPES is always followed by immunosuppression, decrease of quantity and cytotoxic activity of CD8+ and NK-cells and dysfunction of their supervising functions, processes of apoptosis, activation of proinflammatory cytokines and sustentation of not cropped areas of chronic inflammation (Segerstrom, 2005; Lutgendorf et al., 2005; Cohen et al., 2012). All mentioned cases leads to concentration of malignant cells in the body with increase of their invasive potentiality (Sood et al., 2006). CPES adjoints with high risk of development, progress and recurrence of malignant tumors, and the high mortality rate of cancer patients (Thaker et al., 2006; Reiche et al., 2005). The CPES also leads to hippocampal neuronal degeneration as well as to amygdala atrophy (Conrad, 2006), prolonged hypovascularity of the hypothalamo-pituitary-adrenocortical axis (Tsigos and Chrousos, 2002), and accelerated aging of human body (Simon et al., 2006).

So, extensive and deep somatic damaging effect of CPES suggests a significant role of psychogenic factors in the development, recurrence and progression of cancer disease in some cancer patients with psychogenic medical history.

On the basis of the above, it is logical to assume that it is difficult to eliminate the factors compromising the immune system due psychogenic influence and suppression of anti-tumor immunity without effective elimination of persistent tonic descending influences of the central nervous system and the higher nervous activity to the body of cancer patients with psychogenic medical history. Confirmation of dependency of anti-tumor immune activity from higher nervous activity is presented by us as a phenomenon of spontaneous increase of anti-tumor activity of the immune system after the effective relief of psycho-emotional disorders in cancer patients with a psychogenic medical history.

Therefore, advanced cancer patients with psychogenic medical history require a special pathogenetically grounded psycho-immunological recovery in order to restore mental condition, to increase quality of life, to activate an anti-tumor immunity and to block the progression of cancer. The main content of psycho-immunological recovery consists of compliance with a strict sequence of two stages of rehabilitation, which are the phase of psycho-correction and the phase of immunomodulation. The main objective of the first stage of rehabilitation (phase of psycho-correction) is an effective and sustainable elimination of CPES effects which
appear in different psycho-emotional disorders such as anxiety and depression. The main objective of the second phase of recovery (phase of immunomodulation) is the activation of specific anti-tumor immunity.

**METHODOLOGY**

This study had local Ethical committee approval (the Ethical committee of the Institute of Clinical Immunology, Siberian Branch, Russian Academy of Medical Sciences, Novosibirsk, Russian Federation, protocol № 29, August 18, 2004). All patients gave written informed consent.

**Characteristics of cancer patients**

The special psycho-immunological rehabilitation has been offered to 17 patients with advanced cancer (13 women and 4 men). These patients during 5 years (2007 to 2012) had been selected by us among other cancer patients on the following criteria: (1) the progression of the disease, despite that the ongoing standard combination therapy of cancer was provided, (2) the presence of distant metastases (stage IV of cancer), (3) the obvious massive psychotrauma occurred in the lives of patients before being diagnosed with cancer (psychogenic medical history), and (4) informed consent of cancer patients for carrying out rehabilitation. The special clinical case was associated with the patient number 9 (Table 1), who strictly refused to hold a standard combination therapy of cancer, but expressed the strong desire to do her psychological and psychotherapeutic aid. An individual characteristic of cancer patients is presented in Table 1.

**Psychogenic medical history investigation**

Psychogenic medical history has been studied by us in the clinical trial for each patient in medical history of the disease (anamnesis morbi) during first visit to the patient and included the presence of massive psycho-traumatic events (death of the close person, divorce, frequent family conflicts, change of residence, work and appearance of the disabled person in family) with the formation of helplessness and despair.

The mental status examination

The mental-status examination of cancer patients was conducted by the psychiatrist with supplemental usage of all the following psychometrical test systems (for example, The Symptom Checklist 90 (SCL-90) and rates: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychotism, global severity index). The psychiatrist detected the presence or absence of mental disorders in cancer patients in accordance with International Classification of Diseases (ICD-10). Normal values of SCL-90 parameters for healthy people are presented in Table 2 (Tarabrina, 2001). The mental-status examination was administered on the following stages of research: “Before” – before psycho-correction, “After” – after hypnotherapy session and “1 month later” – 1 month later hypnotherapy sessions.

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**Table 1. Characteristics of advanced cancer patients (n = 17).**

<table>
<thead>
<tr>
<th>Patient Nr</th>
<th>Age</th>
<th>Sex</th>
<th>Cancer types</th>
<th>Primary tumor localization</th>
<th>Metastasis localization</th>
<th>Stage</th>
<th>Comorbidities</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>F</td>
<td>Melanoma</td>
<td>Right shoulder</td>
<td>Brain</td>
<td>IV</td>
<td>-</td>
<td>SUR, CHT</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>F</td>
<td>Melanoma</td>
<td>Anterior chest wall</td>
<td>Liver</td>
<td>IV</td>
<td>Urinary stone disease</td>
<td>SUR, CHT</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>F</td>
<td>Melanoma</td>
<td>Anterior abdominal wall</td>
<td>Brain</td>
<td>IV</td>
<td>Chronic cholecystitis</td>
<td>SUR, CHT</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>M</td>
<td>Melanoma</td>
<td>Uveal</td>
<td>Liver</td>
<td>IV</td>
<td>Stomach ulcer</td>
<td>SUR, CHT</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>F</td>
<td>Melanoma</td>
<td>Back skin</td>
<td>Porta hepatitis</td>
<td>IV</td>
<td>Hypertensive heart disease</td>
<td>SUR, CHT</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>M</td>
<td>Melanoma</td>
<td>Anterior abdominal wall</td>
<td>Subcutaneous hands and feet</td>
<td>IV</td>
<td>Stomach ulcer</td>
<td>SUR, CHT</td>
</tr>
<tr>
<td>7</td>
<td>38</td>
<td>F</td>
<td>Melanoma</td>
<td>Skin of temporal region</td>
<td>Retropertoneum</td>
<td>IV</td>
<td>Stomach ulcer</td>
<td>SUR, CHT</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>M</td>
<td>Melanoma</td>
<td>Back skin</td>
<td>Subcutaneous hands and feet</td>
<td>IV</td>
<td>Stomach ulcer</td>
<td>SUR, CHT</td>
</tr>
<tr>
<td>9</td>
<td>55</td>
<td>F</td>
<td>Melanoma</td>
<td>Neck skin</td>
<td>Supraclavicular and axillary lymph nodes</td>
<td>IV</td>
<td>Refuse standard treatment</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>76</td>
<td>F</td>
<td>Kidney cancer</td>
<td>Right kidney</td>
<td>Both lungs, mediastinal and neck lymph nodes, rbs</td>
<td>IV</td>
<td>Hypertensive heart disease, coronary artery disease</td>
<td>SUR, CHT</td>
</tr>
<tr>
<td>11</td>
<td>58</td>
<td>F</td>
<td>Kidney cancer</td>
<td>Right kidney</td>
<td>Left kidney</td>
<td>IV</td>
<td>Hypertensive heart disease</td>
<td>SUR, CHT</td>
</tr>
<tr>
<td>12</td>
<td>53</td>
<td>F</td>
<td>Stomach cancer</td>
<td>Stomach</td>
<td>Porta hepatitis</td>
<td>IV</td>
<td>Stomach ulcer</td>
<td>SUR, CHT</td>
</tr>
<tr>
<td>13</td>
<td>28</td>
<td>M</td>
<td>Stomach and pancreas cancer</td>
<td>Stomach and pancreas</td>
<td>Paraaortic lymph nodes</td>
<td>IV</td>
<td>Stomach ulcer</td>
<td>SUR, CHT</td>
</tr>
<tr>
<td>14</td>
<td>50</td>
<td>F</td>
<td>Breast cancer</td>
<td>Left breast</td>
<td>Skull, ribs, sternum, clavicles, spine, pelvis</td>
<td>IV</td>
<td>Stomach ulcer</td>
<td>SUR, CHT</td>
</tr>
<tr>
<td>15</td>
<td>54</td>
<td>F</td>
<td>Breast cancer</td>
<td>Right breast</td>
<td>Ribs, shoulder joint</td>
<td>IV</td>
<td>Stomach ulcer</td>
<td>SUR, CHT</td>
</tr>
<tr>
<td>16</td>
<td>45</td>
<td>F</td>
<td>Ovarian cancer</td>
<td>Right ovarian</td>
<td>Mediastinal lymph nodes</td>
<td>IV</td>
<td>Stomach ulcer</td>
<td>SUR, CHT</td>
</tr>
<tr>
<td>17</td>
<td>48</td>
<td>F</td>
<td>Lung cancer</td>
<td>Right lung</td>
<td>Left lung</td>
<td>IV</td>
<td>Stomach ulcer</td>
<td>SUR, CHT</td>
</tr>
</tbody>
</table>

SUR – surgery; CHT – chemotherapy; RT – radiotherapy; HYP – hyperthermia.
Correction with medicine of psycho-emotional disorders

The medicinal correction of mental disorders with medicine in advanced cancer patients had been conducted immediately after diagnosis. The antidepressants (tianeptine, venlafaxin), anxiolytics (afobazolm, microdoses of diazepam) and their combination were used. The psychotropic drugs were prescribed for a period of 3 to 6 months to enhance and prolong the therapeutic effect of hypnossuggestive psychotherapy (HSP).

Method of hypnossuggestive psychotherapy

The method of hypnossuggestive psychotherapy is based on strict successive, interconnected, figurative, pathogenetically substantiated suggestive influences in hypnotic states. This method includes followed sessions: (1) Establishment of hypno-rapport between patient and physician; (2) hypnotic de-actualization of psycho-traumatic emotions and experience including a fact of cancer diagnosis; (3) hypnotic lockout of dreams connected with known stress situations which are regularly reproduced in the sleep with the corresponding psycho-vegetative reactions. It is needed for the subject’s exhaustion of psychogenic disorders and to prevent their lingering course; (4) hypnotic reproduction of a personal "health standard" or "health syndrome" – a key session of the whole course of HSP. This "syndrome" is based on using widely known phenomenon of hypnotic hypermnesia (increased memory under hypnosis) generally used for restoration of psychogenic abnormalities of memory. However, it is possible to restore memory of heart beat, respiratory rate, glycemic rate, enzyme reaction activity, and stereotype of digestive system functions from a specific time in the past. The patient recollects the concrete day (date, month, year) from the past – "model, standard" of his health when there was no tumor and he felt well, mentally and physically. In a hypnotic state, suggestions were conducted using the images that are required to retrieve from the memory of cancer patients the "records" that are well known to the body as "health standard". It should be noted that in this key session HSP hypnotic suggestions related to the activation of a great desire, the need for further self-realization in their lives were conducted. In fact, these suggestions were aimed at restoring the loss of life purpose dominant; (5 to 6) the last HSP sessions focused on patients’ education in autohypnosis under suggestive influence. Then patients were given detailed instructions to use autohypnosis for prolongation of the medicinal effect, as well as keeping psychic and vital tone of cancer patients. The duration of the individual course of the HSP was 14 to 16 days.

Evaluation of specific anti-tumor activity of the immune system in advanced cancer patients

Anti-tumor activity of the immune system was assessed by skin test of the delayed type hypersensitivity (DTH) reaction on the tumor-associated antigens (TAA), which were used as a lysed human melanoma cell line BRO (Lockshin et al., 1985) in the amount of 25 thousand cells in a test. Human melanoma cell line BRO was obtained at the Institute of Cytology of Russian Academy Sciences (St. Petersburg, Russia). We investigated the DTH skin reaction after the intradermal administration on the forearm at 9, 12 and 24 h, to identify the peak responses. The peak response in most cases (the diameter of redness in mm) was observed after 12 h. Selection of human melanoma cell line BRO was determined by need to use in one test, the maximum range of TAA to assess the anti-tumor activity of the immune system of patients with different cancers. As shown, there are all kinds of TAA characteristic of solid tumors on the melanoma cells (Wang, 1997).

Selection of the minimal quantity of TAA for the DTH skin test (according to our preliminary studies) was used in order to obtain physiological (not stimulated) specific anti-tumor immunological response as well as in order to exclude the possibility of vaccine’s effect of the diagnostic test itself. In comparison with our colleagues, who used the DTH skin reaction on TAA of human melanoma cell lines in the study of clinical efficacy of anti-tumor polyvalent vaccine “CancerVax” (developed from three allogeneic human melanoma cell lines) (Habal et al., 2001), we used a diagnostic dose which was nearly 100 times smaller (2.5 × 10^6 cells versus 2.4 × 10^8 cells). In addition, our patients did not receive any immunotropic therapy during the study. The selected dose does not cause allergic and other pathological reactions. It is known that the delayed type hypersensitivity reaction is a specific immune response and begins to manifest in 8 to 12 h after ingestion antigen and in most cases the reaction reaches a peak after 48 to 72 h (Carroll, 2011). In our case, the peak responses which is due to the

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**Table 2.** Psychometrical indicators (SCL-90) and DTH skin reaction on TAA in advanced cancer patients before, after and 1 month later after completion of HSP sessions (n = 17).

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Normative values*</th>
<th>Comparative analysis “before-after” and “after -1 month later”</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before (B) mean±SEM</td>
<td>After (A) mean±SEM</td>
</tr>
<tr>
<td>Somatization</td>
<td>0.44±0.16</td>
<td>0.97±0.16</td>
</tr>
<tr>
<td>Obsessive-compulsive</td>
<td>1.12±0.14</td>
<td>0.62±0.10</td>
</tr>
<tr>
<td>Interpersonal sensitivity</td>
<td>0.75±0.04</td>
<td>0.35±0.09</td>
</tr>
<tr>
<td>Depression</td>
<td>0.62±0.04</td>
<td>0.22±0.08</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.18±0.02</td>
<td>0.31±0.01</td>
</tr>
<tr>
<td>Hostility</td>
<td>0.19±0.01</td>
<td>0.43±0.12</td>
</tr>
<tr>
<td>Phobic anxiety</td>
<td>0.51±0.02</td>
<td>0.48±0.07</td>
</tr>
<tr>
<td>Global severity index</td>
<td>4.59±1.2</td>
<td>11.4±2.45</td>
</tr>
</tbody>
</table>

Mean ± SEM – means and standard errors means; *P > 0.05; † - Normative values for healthy people (Tarabrina, 2001).
absence of prior immunization of cancer patients and is the largest contribution of cellular reactions in the DTH skin test were achieved early (within 12 h) (Jacysyn et al., 2001). Evaluation of a specific anti-tumor activity of the immune system in advanced cancer patients was conducted through the research stages: “Before”, “After”, and “one month later”.

Preparation of tumor associated antigens for diagnostic test - DTH skin reaction

The lysed cells of the human melanoma cell line BRO were used as the TAA for diagnostic test. The human melanoma cell line BRO were maintained in RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum, L-glutamine (2 mmol/ml), 25 mmol (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES buffer), and 25 μg/ml gentamicin at 37°C in 5% CO₂ humidified air. Cells were detached from the dish by treating with trypsin-ethylenediaminetetraacetic acid (EDTA) followed by washing three times with Dulbecco’s phosphate-buffered saline, precipitated by centrifuging, counted and diluted with 0.9% saline solution with 0.1% EDTA. Cells were lysed by repeated (8 times) freezing and stored at -80°C until use. As diagnostic test, 2.5 × 10⁸ lysed cells line BRO in 50 microliters was used.

Preparation of tumor associated antigens for epicutaneous activation of specific anti-tumor immunity

The lysed cells of the human melanoma cell line BRO were used as the TAA for epicutaneous activation of specific anti-tumor immunity. The human melanoma cell line BRO were maintained in RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum, L-glutamine (2 mmol/ml), 25 mmol HEPES buffer, and 25 μg/ml gentamicin at 37°C in 5% CO₂ humidified air. Cells were detached from the dish by treating with trypsin-EDTA followed by washing three times with Dulbecco’s phosphate-buffered saline, precipitated by centrifuging, counted and diluted with 0.9% saline solution with 0.1% EDTA. Cells were lysed by repeated (8 times) freezing and stored at -80°C until use. The one epicutaneous activation of specific anti-tumor immunity was performed with usage of 2.5 × 10⁸ lysed cell line BRO in 0.5 ml.

Preparation of tumor associated antigens for extracorporeal activation of specific anti-tumor immunity

The lysed placental cells of domestic pig were used as the TAA for extracorporeal activation of specific anti-tumor immunity. They were obtained by careful mechanical homogenization of placenta without trypsin. Cells were diluted in saline solution supplemented with 0.1% EDTA and 25 μg/ml gentamicin up to concentration of 50 × 10⁸ placental cells in 1.0 ml. Cells were lysed by repeated (8 times) freezing and stored at -80°C until use.

Extracorporeal activation of specific anti-tumor immunity

A peripheral blood mononuclear cell (PBMC), separated from 25 ml of heparinized cancer patient blood have been diluted in RPMI 1640 and supplemented with 20% autologous plasma, L-glutamine (2 mmol/ml), 25 mmol HEPES buffer, and 25 μg/ml gentamicin. PBMC in concentration 4 × 10⁸ cells/ml have been placed in cell culture dish in proportion 1 to 2 × 10⁵ cells/m². The lysed placental cells of domestic pig were used as the antigen in proportion 1/6 (lysed cells of pig placenta/PBMC). This proportion was found as optimal in previous research. Further PBMC with added antigen were placed into CO₂-incubator and incubated at 37°C in 5% CO₂ humidified air. The incubation time was 6 to 8 h for antigen processing by monocytes of PBMC. The PBMC had been collected after completion of incubation by rubber policeman and have been triple-washed in the phosphate buffer solution with added 5% autologous plasma of cancer patient. The washed incubated PBMC were diluted in 2 ml of autologous plasma of cancer patient and shared among two 1 ml syringes. Incubated PBMC were administered subcutaneously in subscapular fossa area and in the area of lower abdomen laterally from umbilicus (palm width sinistral or dextral). Totally three procedures were provided, second provided after two weeks, and the third one after one month since the first procedure.

Epicutaneous (scarification) activation of specific anti-tumor immunity

The superficial line scarifications were applied after skin disinfection on the area of 4 m² with a gap in between lines of 2 to 3 mm wide by blood lancet (scarificator). Damaged area was covered by sterile patch underneath which by syringe was administered a solution with TAA (2.5 × 10⁶ lysed cells line BRO in 0.5 ml). The subclavicular and subcapular areas were used for epicutaneous application of TAA. The exposition of patch with TAA solution left was for 3 days. Four sessions of epicutaneous activation of specific anti-tumor immunity were administered with 14 days break and three sessions were provided with 30 days break.

Statistical analysis

The statistical data processing was done using “BioStat 2009 Professional 5.8.4”, which is publicly available. The level of statistical significance (so-called alpha level for a p-value) was accepted as 0.05. All parameters of investigation were normally distributed (by Kolmogorov-Smirnov test), so in general the parametric tests were used. In order to compare two independent statistical samples the non-parametric Mann-Whitney test was used. The relationship study between psychometrical (SCL-90) and immunological (DTH skin reaction on TAA) parameters was carried out using Pearson's correlation test.

RESULTS

Mental disorders in advanced cancer patients with psychogenic medical history

Clinical studies of 17 advanced cancer patients with psychogenic medical history showed that 100% had a variety of psycho-emotional comorbidity disorders predominantly of anxiety and depression spectrum disorders. The disorders distribution on the base was of ICD-10: generalized anxiety disorder (F41.1) – 3 (patients № 1, 13, 17), mixed anxiety and depressive disorder (F41.2) – 2 (patients № 4, 6), post-traumatic stress disorder (F43.1) – 1 (patient № 7), prolonged depressive reaction (F43.21) – 4 (patients № 3, 8, 12, 16), mixed anxiety and depressive reaction (F43.22) – 6 (patients № 2, 5, 9, 10, 11,14) and organic anxiety disorder (F06.4) – 1 (patient № 15), which in our opinion was a complication chemotherapy. The results of clinical studies of the mental state of advanced cancer patients in general, have been confirmed by the data of psychometry (Table 2, the indicators “Before”).
Psycho-correction stage: Is the first stage of psycho-immunological rehabilitation

The clinical benefits after completion of HSP have been noticed in all advanced cancer patients. It was confirmed by the results of psychometry and comparative analysis, which showed significant improvement in almost all studied parameters (Table 2). Along with a significant improvement in the mental state of cancer patients, a spontaneous increase in specific anti-tumor activity of the immune system has been observed, as determined by DTH skin reaction on TAA ($p < 0.0008$). The sustainability of mental and immunological changes was the main criterion in the decision to move to the next phase of psycho-immunological rehabilitation which is a stage of immunocorrection. In this regard, the studied parameters on the stage “one month later” after completion of the HSP indicated the stability or instability of earlier positive changes. However, in a comparative analysis of indices in the overall group of cancer patients at stages “After” and “one month later” this deterioration was not evident (Table 2). But a careful study of the indicators on the stage “one month later” detected a clear split of cancer patients into two groups by the intensity of DTH skin reaction on TAA (Table 3).

The DTH skin reaction was less than 5 mm in one group of patients, and it was greater than 5 mm in the other group. It was found that cancer patients in these groups differed substantially also in almost all psychometrical parameters. The group of patients with DTH skin reaction less than 5 mm (11 of 17 patients) was characterized by the deterioration of psychometrical indicators, what allowed us to identify this group of patients, as a group with unstable effect of correction of psycho-emotional disorders (patients number 1, 3, 4, 5, 6, 7, 8, 12, 13, 15, 17). Clinically, these patients had worsening of general and mental health, in spite of the use of antidepressants, anxiolytics, and conduct of autohypnosis sessions. Another group of patients whose DTH skin reaction was more than 5 mm (6 patients) differed by maintenance of the previously achieved positive effects of psycho-correction with appropriate psychometrical characteristics. Last group was identified by us as a group of patients with stable effect of psycho-correction (patients' number 2, 9, 10, 11, 14, 16). The close relationship of specific anti-tumor activity of the immune system with the higher nervous activity of cancer patients was confirmed by the correlation analysis between the DTH skin reaction on TAA and psychometrical parameters of SCL-90 on all stages of observation (Table 4).

The dynamics of the relationship showed that medical and psychotherapeutic effect on higher nervous activity of the cancer patients was accompanied by cumulative increase in significant negative correlations between specific anti-tumor activity of immune system and mental well-being of cancer patients. The greatest number of correlations has been observed in 1 month after completion of HSP. Cancer patients with sustained effect of psycho-correction (patient number 2, 10, 11, 14, 16) were proposed as second phase of psycho-immunological rehabilitation (phase immunocorrection), except for patient number 9.

Stage of immunocorrection: The second stage of psycho-immunological rehabilitation

The stage of immunocorrection lasted for 5 months, along with the procedures of activation of specific anti-tumor immunity, advanced cancer patients taking psychotropic medications and performed self-hypnosis sessions. Each procedure of epicutaneous activation of specific anti-tumor immunity was accompanied by local reactions such as redness, pain, and local itching at the injection site. All cancer patients observed pain in the area of metastatic tumor formation (including previously undiagnosed) as well as pain in regional lymphnodes on

### Table 3. A comparative analysis of the studied parameters in cancer patients with unstable and stable effect of correction of psycho-emotional disorders.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Normative value</th>
<th>Unstable effect (n=11) Mean±SEM</th>
<th>Stable effect (n=6) Mean±SEM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatization</td>
<td>0.44±0.03</td>
<td>1.05±0.18</td>
<td>0.32±0.13</td>
<td>0.014</td>
</tr>
<tr>
<td>Obsessive-compulsive</td>
<td>0.75±0.04</td>
<td>0.95±0.13</td>
<td>0.42±0.15</td>
<td>0.024</td>
</tr>
<tr>
<td>Interpersonal sensitivity</td>
<td>0.66±0.03</td>
<td>0.86±0.11</td>
<td>0.20±0.08</td>
<td>0.005</td>
</tr>
<tr>
<td>Depression</td>
<td>0.62±0.04</td>
<td>1.10±0.12</td>
<td>0.35±0.11</td>
<td>0.003</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.47±0.03</td>
<td>0.68±0.10</td>
<td>0.13±0.07</td>
<td>0.003</td>
</tr>
<tr>
<td>Hostility</td>
<td>0.60±0.04</td>
<td>0.50±0.09</td>
<td>0.31±0.15</td>
<td>*</td>
</tr>
<tr>
<td>Phobic anxiety</td>
<td>0.18±0.02</td>
<td>0.33±0.10</td>
<td>0.05±0.03</td>
<td>*</td>
</tr>
<tr>
<td>Paranoid ideation</td>
<td>0.54±0.04</td>
<td>0.71±0.18</td>
<td>0.11±0.04</td>
<td>0.009</td>
</tr>
<tr>
<td>Psychoticism</td>
<td>0.30±0.03</td>
<td>0.57±0.10</td>
<td>0.12±0.07</td>
<td>0.007</td>
</tr>
<tr>
<td>Global severity index</td>
<td>0.51±0.02</td>
<td>0.82±0.11</td>
<td>0.23±0.07</td>
<td>0.004</td>
</tr>
<tr>
<td>DTH skin reaction on TAA, mm</td>
<td>not defined</td>
<td>1.91±0.53</td>
<td>17.3±2.55</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Mean ± SEM – means and standard errors means; *P > 0.05; † - Normative values for healthy people (Tarabrina, 2001).
the 3rd day, sometimes increased body temperature to 37°C, deterioration of health in the form of weakness, lethargy and sleepiness. In order to relief these reactions, patients received Nise (nimesulide) tablets 100 mg, 2 times a day for 5 to 7 days. Procedures of extracorporeal activation of specific anti-tumor immunity also accompanied by systemic reactions, but clinically less severe than with procedures of epicutaneous activation. In addition, local reactions were observed such as redness, pain and itching at the site of local administration.

Catamnesis

The advanced cancer patients with unstable clinical effect of the correction of the psycho-emotional disorders (patient № 1, 3, 4, 6, 7, 8, 12, 13, 15, 17) died within 2 to 5 months since psycho-correction stage had been over, except patient № 5 who had died after one year. These advanced cancer patients are likely to have had more pronounced somato-psychic disorders that were not consistently removed with psycho-correction techniques and failed to have influenced anti-tumor immunity. Among the advanced cancer patients that were subjected to psycho-immunological rehabilitation (patient No. 2, 10, 11, 14, 16) the following results were observed. Patient № 2 is alive, catamnesis contains 5 years, a year after the psycho-immunological rehabilitation was over, the symptoms of hemangioma were revealed in the place of liver metastasis (on the basis of the ultrasonic examination data). Patient № 10 is alive; catamnesis was 5 years without substantial negative dynamics. Multiple foci of fibrosis and calcification were discovered by computed tomography. Patient № 11 is alive, catamnesis was 6.8 years after psycho-immunological rehabilitation had finished. A very interesting fact was revealed during the research. After massive stress (she found out about her daughter’s drug addiction), the quick development of the cancer disease was observed and within 7 days the size of the metastasis in the only kidney increased from 38 x 23 mm to 41 x 32 mm. After the effective relief of the psycho-emotional disorders, metastasis regression to 12 x 11 mm was observed. Patient № 14 is alive, catamnesis was 1.5 years. Multiple foci of osteosclerosis without negative dynamics were observed (on computed tomography). Patient № 16 is alive, catamnesis was 4 years. Negative dynamics is not observed, pneumosclerosis foci and extensive fibrotic process are observed in the mediastinum (on computed tomography).

Clinical case (patient № 9)

We have observed the unique clinical case of the cancer patient with malignant melanoma who refused to hold mutilating surgery and chemotherapy, but approached us for psychological help. The patient number 9 was 55 years old, and an accountant. In autumn 2004, melanoma localized on the neck on the left, was histologically verified. The patient turned to us on 20th January, 2005. It was examined that the patient had the primary focus (40 x 35 mm) and multiple metastases in the neck (20 mm), supraclavicular (35 mm) and axillary (20 mm) lymph nodes on the left (Figure 1). Ultrasound examination of the primary tumor revealed that the depth of tumor invasion in the tissues of the neck is 25 mm. After examination, the patient was diagnosed a psychogenic medical history (she lives with a disabled husband, who is alcoholic), mixed anxiety and depressive reaction (F43.22) and the lack of inhibition of specific anti-tumor activity of the immune system, defined by the absence of DTH skin reaction on TAA. We observed that the patients with a similar localization of melanoma died within 4 to 6 months due to profuse bleeding from the

<table>
<thead>
<tr>
<th>Indicator</th>
<th>DTH skin reaction on TAA, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
</tr>
<tr>
<td>Somatization</td>
<td>0.13</td>
</tr>
<tr>
<td>Obsessive-compulsive</td>
<td>-0.27</td>
</tr>
<tr>
<td>Interpersonal sensitivity</td>
<td>-0.09</td>
</tr>
<tr>
<td>Depression</td>
<td>-0.09</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-0.10</td>
</tr>
<tr>
<td>Hostility</td>
<td>-0.06</td>
</tr>
<tr>
<td>Phobic anxiety</td>
<td>-0.16</td>
</tr>
<tr>
<td>Paranoid ideation</td>
<td>-0.31</td>
</tr>
<tr>
<td>Psychoticism</td>
<td>-0.22</td>
</tr>
<tr>
<td>Global severity index</td>
<td>-0.14</td>
</tr>
</tbody>
</table>

Table 4. The correlation analysis between the DTH skin reaction and psychometrical indicators of SCL-90 in advanced cancer patients with psychogenic medical history on stages of observation (n=17)
tumor foci and frequent metastasis to the brain. From January 21st to February 4th, 2005, the patient had undergone a course of hypnotherapy consisting of 4 treatment sessions and 2 sessions of self-hypnosis training. After treating the patient with HSP (5th February, 2005), along with the improvement of general state of health and relief of anxiety and depressive disorders, positive changes in a number of objective indicators were seen. Thus, DTH skin reaction on TAA increased from 15 mm (before HSP) to 40 mm (after HSP) and maintained for 2 days, the absolute number of peripheral blood lymphocytes increased 3 times: from 709 to 1 mm³ (before HSP) up to 2244 in 1 mm³ (after HSP). In addition, there was a change of the vegetative (autonomic) nervous system, which was assessed by heart rate variability (HRV) (Task Force, 1996). HRV is the assessment of individual differences in emotional reactions, particularly in relation to social processes and mental health (Appelhans and Luecken, 2006). The indicator of the total power (TP of HRV) at the spectral analysis increased 20-fold: from 213 ms² (before HSP) to 4260 ms² (after HSP). In addition, there was a reduction of ratio of LF/HF (normalized units) 5-fold: from 2.76 (before HSP) to 0.53 (after HSP), indicating a change of state of sympathicotonia to the state parasympathicotonia and this is a confirmation of the clinical fact of depression relief (Giese-Davis et al., 2006).

After the completion of HSP, the patient conducted daily self-hypnosis sessions in accordance with our proposed program, the content of which was aimed at forming a dense impermeable capsule around the tumor foci, which like a “plaster cocoon walls up, squeezes and strangles tumor foci.” After several self-hypnosis daily sessions lasting 1 h each, the pronounced swelling of the left side of the neck and supraclavicular area with the transition to the chest were observed (Figure 2), body temperature rose up to 38°C, and itching of tumor foci appeared. The patient reported that “stifling of the tumor” started. Within 8 days, the swelling completely disappeared, along with a decrease in the size of metastatic lymph nodes in the neck, supraclavicular and axillary regions. The patient continued, nearly on a daily basis, to use self-hypnosis according to organic-oriented suggestive program “stifling of tumor foci.” Nine months after (03 November, 2005) the beginning of organic-oriented therapeutic autosuggestion, the patient underwent ultrasound examination of the tumor foci. The results showed regression of metastatic lymph nodes in the neck, in the supraclavicular and axillary regions. A fibrous capsule (Figure 3) was formed deep in the tissues of the neck throughout the borders of tumor invasion of primary tumor focus, which actually corresponds to the content of curative autosuggestion. Further observation showed that endophytic growth of the primary tumor focus changed to exophytic growth (tumor acquired an exophytic form on the leg with a base of 23 mm) with the regression of metastatic lymph nodes in the neck, in supraclavicular and axillary regions (Figure 4). Hereinafter, a slow progression of the cancer process with a gradual increase of phenomena cachexia was observed. The patient died on 14th April, 2008. Despite the expected death, it may be stated that the cancer patient had been able to live an active life for 3 years without the operation of the neck melanoma.

Figure 1. Localization of malignant neck melanoma, patient N9.

Figure 2. Pronounced swelling of the neck tissues after organic-oriented self-hypnosis sessions.
Neck skin’s surface 
Fibrous capsule formation 
Primary 
tumor 
03 Nov 2005 

Figure 3. Fibrous capsule around the primary tumor in the depth of the tissues neck after self-hypnosis sessions (ultrasound data).

Figure 4. Exophytic growth of melanoma with metastases regression in the lymph nodes of the neck and supraclavicular area against self-hypnosis treatment sessions.

DISCUSSION

The peculiar properties of mental disorders in advanced cancer patients with psychogenic medical history

The study of psychogenic medical history showed that all patients were in the state of obvious emotional stress before cancer diagnosis (in average of 1.5 years), which was caused by massive psycho-traumatic events. This is a long-term emotional tension accompanied by the formation of the feeling of helplessness, hopelessness, despair. We can assert that these future cancer patients long before the diagnosis of cancer have already had psychogenically caused psycho-emotional and psychosomatic disorders. The diagnosis of cancer itself is an additional massive and inexhaustible psychotrauma, emotionally paralyzing fear, so-called “Damocles syndrome” (Koocher and O’Malley, 1981).

The cancer patients with psychogenic medical history are patients with doubled massive psychotrauma. Undoubtedly, advanced cancer patients with psychogenic medical history had somatopsychic disorders along with cancer progression, so these patients were observed with clinically difficult to differentiate combination of psychosomatic and somatopsychic disorders. The main feature of psychiatric disorders in cancer patients with psychogenic medical history that we have found is the fact that, despite the urgency of the massive psychotrauma and other conditions for the development of neuroses (known as neurotic “Jaspers’ triad”), the cancer patients show the condition which is opposite to neurosis and can be defined as a state of “deneurotization”. This phenomenon is clinically manifested by blurry, non deployed and tarnish mental symptoms, and cancer patients themselves do not consider their mental condition as sick and perceive it as quite natural, situationally understandable, though very painful, subjectively. This deneurotization syndrome is hard to define according to DSM-IV or ICD-10.

In addition, some advanced cancer patients are observed with conditions of dissociative disorders that manifest themselves through inconsistency of psychometrical assessments to clinical studies. In other words, the psycho-emotional disorders in a clinical study are obvious, but psychometrical parameters are within the normal limits. The deneurotization and dissociative disorders can insidiously hide the true extent of the level...
of psychopathology in advanced cancer patients and may be the cause of undiagnosed mental disorders. Thus, the study of psychiatric morbidity with self-report screening instrument without clinical examination does not provide a fair view of psychopathology in cancer patients.

**HSP as a method of choice for the quick correction of mental disorders in advanced cancer patients**

For the fastest and effective correction of psycho-emotional disorders in advanced cancer patients, combination approach was selected, which involves the simultaneous use of psychotropic drugs, and hypnotherapy. This approach was driven by the severity of psychopathology of advanced cancer patients and the possibility of rapid progression of the cancer disease. It should be noted that hypnotherapy differs from other methods of psychotherapy by high efficiency and velocity of clinical benefit achievement including oncology (Montgomery et al., 2013). Thus, the comparative analysis has shown that after 600 sessions of psychoanalysis, 38% of patients reported feeling better, after 22 sessions of behavioral therapy, 72% of patients reported a positive result, and after 6 sessions of hypnotherapy, 93% of patients referred to the desired effect (Barrios, 1970). Our 25-years clinical experience confirms the major clinical capabilities of hypnossuggestive psychotherapy in the correction of mental and psychosomatic disorders. In particular, we first discovered the phenomenon of psychogenic mobilization of CD34+CD38- stem cells (Bukhtoyarov et al., 2006) and an increase in telomere length in peripheral blood mononuclear cells in cancer patients during hypnotherapy (Bukhtoyarov et al., 2008). Later, this phenomenon to some extent has been confirmed by other researchers using psychosocial telephone counseling intervention (Biegler et al., 2012). It should be noted that because of the state of hypersuggestiveness of advanced cancer patients there is a risk of formation of hypnotic dependence (hypnomania), so the number of HSP sessions was limited to 6 sessions of hypnotherapy.

**DTH skin reaction on TAA as a biomarker of removing mental disorders**

It can be assumed that the spontaneous increase in specific anti-tumor activity of the immune system, as determined by DTH skin reaction on TAA, reflects a relief of psychogenic immunosuppressive effects of higher nervous activity on the anti-tumor activity of the immune system of advanced cancer patients. Actually, DTH skin reaction appeared to be a kind of biological marker of the presence or absence of psycho-emotional disorders in advanced cancer patients with psychogenic medical history. It can be assumed that the initial absence of correlation between DTH skin reaction and psychometrical parameters likely was caused by the disintegration processes in the organism of advanced cancer patients inter alia by violation of the interaction of the two main integrative systems of the body which are the nervous and immune systems. The systemic impact (medication and psychotherapy) on higher nervous activity in cancer patients is accompanied by gradual recovery of damaged linkages between the nervous and immune systems of the body. These data indicate a significant effect of the higher nervous activity on to the antitumor activity of the immune system of advanced cancer patients with psychogenic medical history.

**Features of immunocorrection**

The main task of the immunocorrection stage was stimulating of the specific anti-tumor immunity of advanced cancer patients by immunological methods after spontaneous increase of their immune system anti-tumor activity as a result of sustained relief of psycho-emotional disorders. Presumably, the effective activation of the specific anti-tumor immunity had to have a positive impact on the course of the cancer disease. Therefore we deliberately developed a method of epicutaneous (scarification) activation of specific anti-tumor immunity and extracorporeal activation method using a small amount of peripheral blood. Both methods in the preliminary studies have shown high effectiveness and safety in clinical practice (unpublished data). It should be particularly noted that the very low dose of TAA, moreover introduced epicutaneous, had led to systemic reactions of the whole body. It can be assumed that such clinical effect was due to the specific systemic immune responses that are associated with the capture TAA by antigen-presenting epidermal Langerhans cells and migration of these cells to regional lymph nodes and antigen-presenting TAA. The latest data shows greater potential of CD8+ cells activation by Langerhans cells (Polak et al., 2012). The antigen-presenting TAA in the lymph nodes leads to activation and clonal expansion of antigen-specific T cells and the subsequent development of specific inflammation in metastatic tumor foci. We observed systemic clinical manifestations of these processes on the third day.

**Mind and tumor encapsulation**

Scientific and clinical evidence shows that cancer has always been primarily a local tissue process. Ideally, the focus of the tumor should be immunogenic and is supposed to be recognized by the immune system as allogenic and thus, to be localized (delimitated) and destructed by the cell-effectors of specific anti-tumor immunity. In this case, encapsulation process is a universal
natural mechanism of localization of anything allogenic in the body. This fully applies to the localization of malignant tumor formation. A fibrous capsule of different density around the tumor foci have always been observed in experimental animals. It is interesting that the structure of the extracellular macromolecule matrix in capsules around the malignant and benign tumors do not differ (Grigioni et al., 1990). In clinical practice, we can often see a favorable course of cancer regardless of the tissue localization when dense fibrous capsule around the tumor foci are formed. Actually, the formation of fibrous capsule is associated with low levels of cancer recurrence and a capsule can serve as a mechanical and chemical barrier to metastasis (Lunevicius et al., 2001).

Other authors in clinical practice found that the encapsulation of the tumor was an important favorable prognostic factor for survival without signs of cancer disease (Sherratt, 1999). In this regard, we have developed organic-oriented treatment program for self-hypnosis, which presumably could have a decreased trophic’s effect on the tumor tissue and contribute to the induction of tumor encapsulation. The examined clinical case confirms what is known about the significant impact of the brain and higher nervous activity on cancer (Mravec et al., 2008). Furthermore, this case presents new data on the possible trophic effects on the tumor tissue and on suppressing the cancer process by the deliberate action on the higher nervous activity in cancer patients.

The role of the mind in generalization of the cancer process, the phenomenon of "reparative trap"

The cellular and molecular factors and mechanisms of cancer’s generalization have been presented in detail nowadays, the determinants of invasiveness and the invasion-metastasis cascade have been studied (Weinberg, 2008), the tumor-induced immunosuppressive network have been shown (Kim et al., 2006). There is also evidence that biobehavioral risk factors such as social adversity, depression, and stress are involved in cancer progression (Lutgendorf and Sood, 2011; Spiegel, 2012). Researchers found a 30-fold increase in cancer spread throughout the bodies of stressed mice, compared with those that were not stressed. Chronic stress acts as a sort of fertilizer that feeds breast cancer progression, significantly accelerating the spread of the disease in animal models (Sloan et al., 2010; Moreno-Smith et al., 2010). It can be argued with a certain degree of confidence that chronic stress is also a kind of fuel for growth and generalization of human cancer.

The results of this study suggest that the decisive role in the generalization of the cancer process for the category of advanced cancer patients with psychogenic medical history is the psychogenic factor. This factor is shown in the form of psychogenically determined mental disorders (depressive and/or anxiety disorders), which activate and maintain the cellular and molecular mechanisms of carcinogenesis, and open the way to the generalization of the cancer process (Figure 5). As it is seen in Figure 5, the psycho-emotional disorders (depressive and/or anxiety disorders) in cancer patients during CPES are accompanied by the disintegration of the major systems in the brain (Shumake and Gonzalez-Lima, 2003), in particular, persistent presence of over-active on sympathetic-adrenal-medullary and hypothalamic-pituitary-adrenal systems. In the state CPES, the central nervous system exerts downward tonic effect on the “target organs”, accompanied by permanent disturbances of micro-circulation to form in the tissue where the cell’s damage occurred (including DNA damage) by the products of oxidative-nitrosative stress (endogenous mutagens). Permanent tissue damage in the body simultaneously accompanied sanogenic processes in order to repair damaged tissue with mandatory reciprocal inhibition of anti-tumor immunity for tissue healing. This is due to the fact that the restoration of normal tissue proliferating cells always express a number of tumor-associated antigens, so in case of high activity of anti-tumor immunity, repair processes would be difficult, since normal proliferating cells would be recognized as tumor-transformed.

Reparative focus of the immune system of cancer patients with psychogenic medical history is shown in a shift of balance T-helper-1/T-helper-2 lymphocyte subpopulations in the predominance of T-helper-2 lymphocyte subpopulations and the significant increase in the tissues of alternatively activated macrophages (M2 macrophages). These M2 macrophages are secrete IL-10, CCL17, CCL22, CCL18, IL-1RA, and IL-1R decoy. M2 macrophages are active workers of the host, promoting scavenging of debris, angiogenesis, remodeling, and repair of wounded/damaged tissues (Solinas et al., 2009). It is known that alternatively activated macrophages in tumor foci orient the immune response towards the activation of repair of processes in cancer centers, supports them in inflammation and angiogenesis, that is determine tumor growth and metastasis (Pollard, 2004). In tumor foci M2 macrophages take up to 50% of the tumor mass (Gordon and Martinez, 2010). It should be particularly noted that the induction of M2 macrophages is influenced by stress hormones – corticosteroids (Solinas et al., 2009). Thus, there is every reason to believe that the growth of the tumor and the generalization of cancer in the body of cancer patients with psychogenic medical history are determined by the phenomenon of reparative focus (direction) of their immune system. In general, the presented pathophysiological process in psychogenic carcinogenesis can be called “reparative trap” by the organism when the permanent tissue damage requires constant repair with appropriate suppression of antitumor immunity. Any additional damage in the body of a cancer patient with psychogenic carcinogenesis, including surgery, chemotherapy radiation therapy, enhances the phenomenon of a "reparative trap".
Our clinical observations suggest that cancer patients in general (and with psychogenic medical history in particular) no more and not longer than healthy people suffer colds, bacterial and fungal diseases. This points to the selective suppression of anti-tumor immunity, but not total compromising the immune system of cancer patients. Moreover, almost all cancer patients note a common or even accelerated healing of wounds, cuts, and scratches. These clinical data also reflect the reparative orientation of the immune system of cancer patients. In our view, the need to prove empirically the categorical prohibition of any cancer patient physiotherapy, enhancing tissue repair processes in the body, is connected with this phenomenon. The above mentioned fully applies to some psychotherapy. In particular, in cancer patients with not eliminated psycho-emotional disorders, the use of various relaxation techniques, as well as self-hypnosis or suggestion of warmth, improvement of blood supply and other trophically oriented therapeutic suggestion result in rapid progression of the cancer process. Moreover, cancer patients with non eliminated psycho-emotional disorders relaxed at the spa, in the tourist trip to relieve stress, relax, escape, recover, and often lead to progression of the cancer process shortly after returning home. Thus, the generalization of cancer in cancer patients with psychogenic medical history depends on the availability of non eliminated psycho-emotional disorders associated with compromising their anti-tumor immunity. In this regard, early detection and relief of psycho-emotional disorders in cancer patients with psychogenic medical history could prevent the transition of these patients in the category of advanced cancer patients. At the same time, advanced cancer patients with psychogenic medical history may have more favorable prognosis after they receive pathogenetically substantiated psycho-immunological rehabilitation.

**Conclusion**

The present study revealed that there is a special group of advanced cancer patients by the presence of their psychogenic medical history, comorbid psycho-emotional disorders, and suppressed specific anti-tumor activity of the immune system. Mentioned above characteristics we believe are the clinical criteria of the psychogenic (stressful) carcinogenesis. So, a co-morbid psycho-emotional disorders of this group of the advanced cancer patients have the major influence on the course and the outcome of the cancer disease. These patients need to hold a special psycho-immunological rehabilitation, consisting of two strictly sequential steps: elimination of psycho-emotional disorders, and activation of specific anti-tumor immunity. At the same time, the impossibility of sustained relief of psycho-emotional disorders in advanced cancer patients on the first stage of rehabilitation exclude further transition to immunological recovery phase and can be considered as an adverse prognostic factor with regard to the life of these patients. The results of this study are preliminary and require further clinical evidence on a larger contingent of patients with cancer and may be interested to various professionals involved in treating advanced cancer patients.

**ACKNOWLEDGEMENTS**

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**Abbreviations**

CPES, Chronic psycho-emotional stress; DTH, delayed

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**Figure 5.** The role of chronic stress (mental disorders) in the generalization of the cancer process in patients with psychogenic medical history. (A) Psycho-emotional disorders (anxiety, depression) as a result of chronic stress in cancer patients with psychogenic medical history are accompanied by permanent damage to body tissues and compensatory systemic activation of sanogenic processes to repair damaged tissue. These system recovery processes are inevitably accompanied by systemic suppression of anti-tumor immunity, paving the way for the generalization of the cancer process. (B) Sustainable relief of psycho-emotional disorders in cancer patients restores the natural system activity of anti-tumor immunity and promotes the localization of the cancer process.
type hypersensitivity; TAA, tumor-associated antigens; HSP, hypnosophic psychotherapy.

REFERENCES


Full Length Research Paper

Sun avoidance among indoor employees leading to vitamin D deficiency and depression in the United Arab Emirates

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Vitamin D deficiency has been linked to chronic diseases among different populations worldwide. However, these relationships are still unclear and have not been explored within the United Arab Emirates (UAE) population. In this study, the relationship between vitamin D, risk for depression symptoms, and sun avoidance inventory was explored. The prevalence of vitamin D deficiency among a sample of employees working in Abu Dhabi (the capital of UAE) was first assessed and then the influence of demographic factors (age, gender and ethnicity) on vitamin D status was examined. A random sample of 141 employees from two different major oil companies within Abu Dhabi was selected and tested for vitamin D deficiency. All participants worked indoors and reflected the multi-ethnic nature of Abu Dhabi residents. Serum levels of vitamin D [25(OH)D] were measured and depression was assessed using the Beck Depression Inventory version 2. Moreover, the sun avoidance inventory (SAI) was used to assess attitudes towards sun avoidance in the context of vitamin D deficiency. There was a significant negative correlation between vitamin D levels and sun avoidance scores (r=-0.45, p<0.0001). Sun avoidance scores were also significantly positively correlated with depression symptoms scores (r=0.33, p<0.001). This study demonstrated that sun avoidance behaviors were the major risk factor for vitamin D deficiency among Abu Dhabi employees and that these were also positively associated with depressive symptoms.

Key words: Vitamin D deficiency, United Arab Emirates, indoor employees, sun avoidance inventory, Beck depression inventory.

INTRODUCTION

The role of vitamin D in maintaining optimal health has been well established (Holick, 2009). Nonetheless, vitamin D deficiency has reached epidemic levels in many parts of the world, affecting both genders across all age groups (Holick, 2004, 2005; Holick et al., 2011). Populations at risk of deficiency include those with decreased sun exposure due to limited outdoor activities. The list of individuals meeting these criteria is extensive, indoor-workers, students and even those who extensively apply sunscreens or wear extensive clothing when exposed to the sun (Holick, 2004; Grant, 2009; Glerup et al., 2000).

Sun avoidance among many individuals, is attributable
to the arguably, iatrogenic public health messages focused on the adverse effects of sun exposure. Such messages generally ignore the potential benefits of sun exposure. Such warnings focus public attention on the adverse consequences associated with exposure of ultraviolet (UV) radiation such as melanoma and skin aging (Grant, 2007). In the past few decades however, research has also documented many benefits associated with exposure to UV radiation, highlighting the necessity of adequate sun exposure for healthy vitamin D levels. There is growing evidence supportive of the protective role vitamin D plays in seasonal variations in depressive symptomatology. In some nations, depression is more common during the winter, which parallels the nadir for vitamin D deficiency as well. Two recent studies explored the relationship between vitamin D levels and depression among older adults (Hoogendijk et al., 2008; Wilkins et al., 2009). These studies compared the level of vitamin D among depressed and non-depressed individuals, and found vitamin D levels to be significantly lower in depressed individuals compared to non-depressed individuals (Hoogendijk et al., 2008; Wilkins et al., 2009).

There are relatively few studies exploring vitamin D and its health implications within the context of the United Arab Emirates (UAE). Despite the availability of sunshine in the UAE, vitamin D deficiency represents a critical maternal/infant health problem. A study conducted at Al-Ain, UAE, showed that vitamin D deficiency (serum level, 25 ± 11 nmol/L) is common (36% frequency) in women of childbearing age (n = 33) in Arab communities residing in the UAE (Dawodu et al., 2001, 1998). Vitamin D deficiency is a common maternal-infant health problem in Arab communities residing in Al-Ain, UAE (Dawodu et al., 1998). Moreover, osteoporotic Emirati women suffer from mild to severe vitamin D deficiency (Saadi et al., 2006). A recent study undertaken in the Emirate of Abu Dhabi, UAE, found a high prevalence of vitamin D deficiency among young adult Emirati University students associated with self-reported sun avoidance behaviors (Al Anouti et al., 2011). Furthermore, in the region’s first study exploring the relationship between depressive symptoms and vitamin D levels, a study of university students in Abu Dhabi found a negative correlation between vitamin D levels and depressive symptomatology (Thomas et al., 2010). This study aims to explore the relationship between vitamin D deficiency, depression symptoms, and sun avoidance behaviors among indoor workers residing in Abu Dhabi.

SUBJECTS AND METHODS

Study population and design

A total of 141 employees from two different major oil companies within Abu Dhabi participated in the study. The rationale behind choosing oil companies was their willingness to cooperate and improve the health of their employees. In addition, being major companies, their employees are representative of the employee subpopulation within Abu Dhabi. Convenience sampling was applied; participants were recruited voluntarily through electronic invitation cards that were sent to all employees a week before data collection. The study recruitment was conducted in October 2010 and May 2011. A certified phlebotomist collected blood samples. The Zayed University Human Subjects Committee and the Sheikh Khalifa Medical City Institutional Review Board approved the study. Written informed consent was obtained from all participants before study enrollment. Participation in the study was completely voluntary and confidential.

Analysis of serum 25(OH)D

Blood samples were taken from all subjects to analyze serum 25(OH)D as an indicator of vitamin D status (Haq et al., 2007; Haq et al., 2008). Questionnaire was offered in both Arabic and English. Serum concentrations of 25(OH)D were measured at two different techniques e.g., Diasorin (LIAISON), and high performance liquid chromatography (HPLC). The LIAISON 25(OH) vitamin D assay is a direct competitive chemiluminescence immunoassay (CLIA) for quantitative determination of total 25(OH)D in serum. Waters HPLC 2695 separation module with UV detection based Chromsystems kits (Chromsystems Instruments & Chemicals GmbH, Heimburgstrasse, Munich, Germany) was used as modified in our laboratory (Haq et al., 2009; Thomas et al., 2011). The intra-assay coefficient of variation was 4% and the inter-assay coefficient of variation was 5.8% (Al Anouti et al., 2011).

Exposure variables

Sun exposure was evaluated by using SAI, which is a questionnaire designed to assess attitude toward sun avoidance (Al Anouti et al., 2011; Thomas et al., 2010). Data collection involved a blood test and a previously validated questionnaire that had several components pertaining to socio demographic, medical history, and psychosocial aspects (Beck Depression Inventory (BDI) and Sun Avoidance Inventory (SAI)) (Thomas et al., 2010). The SAI assesses sun avoidance attitudes and behaviors across six factors: cosmetic/aesthetic, health and safety, transport, occupational, recreational and sartorial. The SAI uses a five point Likert scale to record participant’s responses, from strongly agree, to strongly disagree, graded 0 to 4 depending on the item direction. A high overall score on the SAI indicates that the individual minimizes sun exposure, while a low score reveals that the individual maximizes exposure to sun (Thomas et al., 2010). Body mass index (BMI) was calculated as weight in kilograms divided by the height in meters square. Depression was assessed by using BDI (Beck et al., 1996a). The reason for using BDI is that it is one of the widest used measures of depressive symptomatology used in the research literature. Its psychometric properties have been extensively explored in both English and Arabic. The BDI is a 21-item self-report inventory assessing the severity and intensity of depressive symptoms. Each item reflects either a cognitive or somatic symptom of depression; items are rated from 0 to 3, with higher scores reflecting heightened symptom severity. The cognitive sub scale was obtained by summing 9 items, whereas the somatic-affective sub scale was obtained by summing 11 items. Amongst North American college students and hospital outpatients, BDI-II was found to have high internal consistency; the coefficient alphas were 0.93 and 0.92, respectively (Beck et al., 1996a, b). Subsequent studies of the BDI’s psychometric properties report favorably on the instrument’s construct, convergent, and predictive validity, in various contexts, and across several nations (Al-Musawi, 2001). Questionnaire was administered by a single research assistant within the time frames. Both oil companies were located within the same geographic location in Abu Dhabi. All participants in
Table 1. Baseline characteristics of the employees that participated in the study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Median</th>
<th>25-75 P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>141</td>
<td>43</td>
<td>35-49</td>
</tr>
<tr>
<td>*BDI</td>
<td>110</td>
<td>5</td>
<td>1-9</td>
</tr>
<tr>
<td>*BMI</td>
<td>102</td>
<td>26.2</td>
<td>24-29</td>
</tr>
<tr>
<td>SAI</td>
<td>103</td>
<td>41</td>
<td>36-46</td>
</tr>
<tr>
<td>*25(OH)D nmol/L</td>
<td>141</td>
<td>22.4</td>
<td>17-31</td>
</tr>
</tbody>
</table>

All values are shown as median and inter-quartile range (25-75 P); BMI: Body mass index; SAI: sun avoidance inventory; BDI: Beck depression inventory. *Non normal distribution.

Figure 1. Group distribution according to vitamin D status among employees.

RESULTS

The median age (IQR) of participants was 43 (35 to 49) years. Amongst the 141 participants, 23 were UAE nationals, 47 were non-Gulf Arabs, 7 Europeans, 2 Canadians and 62 were South Asians. Participants were from different ethnicities and from both genders (88% males and 12% females). Table 1 shows the distribution of the variables: age, BDI, BMI, SAI and vitamin D status among all participants. Based on the median (IQR) for BMI, most subjects showed only minimal levels of depressive symptoms (1 to 9). The median (IQR) BDI was 26 (24 to 29) with approximately 40% being overweight. Median (IQR) serum 25(OH)D concentration was 22 (17 to 31) nmol/L. Group distribution according to vitamin D status is as shown in Figure 1.

Only 2.1% of the participants (3 out of 141) were sufficient (serum 25(OH)D>75 nmol/L). All other participants were severely deficient (63.2%), deficient (29.1%)
or insufficient (5.7%). The median (IQR) SAI of 41 (36 to 46) indicated that most participants significantly avoided exposure to the sun. Bivariate correlations revealed a negative correlation between vitamin D levels and SAI scores ($r=-0.45$, $p<0.0001$). Sun avoidance scores were also significantly positively correlated with depression symptoms scores (BDI) ($r=0.32$, $p<0.001$). On further analysis into cognitive and somatic BDI sub scale scores, it was found that the cognitive component of BDI was moderately correlated with SAI ($r=0.03$, $p<0.001$) whereas the somatic component of BDI was not correlated ($p=0.09$). There was no statistical difference in vitamin D levels between participants scoring in the subclinical BDI range or in the range of minor depression. There was no significant correlation between age and depression ($r=-0.16$, $p<0.08$). SAI scores were negatively correlated with age ($r=-0.27$, $p<0.01$). Table 2 reports the correlation between all relevant variables. Females had significantly higher depression scores than males ($p=0.0003$) and lower SAI ($p=0.009$) and vitamin D concentrations ($p=0.003$). These comparisons are demonstrated in Box and Whisker plots in Figure 2.

**DISCUSSION**

The findings in this study suggest that vitamin D deficiency is prevalent among indoor employees within Abu Dhabi. The nature of work is associated with limited sun exposure, official working hours for most employees being between 8.00 am to 4.00 pm. Hence, employees spend most of the daytime (10.00 am to 3.00 pm) which is the optimum time for vitamin D production indoors. Guidelines of what constitutes healthy versus unhealthy levels of vitamin D are controversial. Various risk factors (e.g. limited sun exposure, inadequate intake of vitamin D, obesity and ethnicity) could account for the high prevalence of vitamin D deficiency (Grant et al., 2010). In the UAE and according to previous studies, these findings suggest that sun avoidance behaviors contributed to the prevalence of vitamin D deficiency. People in the UAE may not only intentionally avoid sun (because of extreme heat), but also may be at risk as a result of the cultural and traditional dress codes that minimize the body’s exposure to the sun. This may explain why all UAE national (both males and females) had low vitamin D levels. Sun deprived individuals, such as indoor employees, who require 800 to 1000 IU of vitamin D daily to attain optimal vitamin D levels (Holick et al., 2011).

Approximately 23% of the participants suffered from chronic diseases, particularly hypertension and diabetes. Fourteen were hypertensive, six were diabetic, three were both hypertensive and diabetic, and two suffered from hypercholesterolemia. The correlation between vitamin D deficiency and these chronic illnesses warrants further evaluation for possible causality. Further exploration is necessary however, before any conclusions could be made.

Interestingly, the results demonstrated that depression is positively correlated with sun avoidance behaviors. The association can be looked at differently; sun avoidance behaviors could lead to depression or depression could

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**Table 2. Correlation between variables in the context of 25(OH)D.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation Coefficient</th>
<th>Age</th>
<th>BMI</th>
<th>BDI</th>
<th>SAI</th>
<th>25(OH)D (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>-</td>
<td>0.06</td>
<td>-0.17</td>
<td>-0.25</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Significance Level P</td>
<td>0.51</td>
<td>0.080</td>
<td>0.01</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>102</td>
<td>110</td>
<td>101</td>
<td>141</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>0.06</td>
<td>-</td>
<td>-0.04</td>
<td>-0.16</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Significance Level P</td>
<td>0.51</td>
<td>-</td>
<td>0.68</td>
<td>0.13</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>102</td>
<td>102</td>
<td>94</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>BDI</td>
<td></td>
<td>0.17</td>
<td>-0.040</td>
<td>-</td>
<td>0.33</td>
<td>-0.11</td>
</tr>
<tr>
<td></td>
<td>Significance Level P</td>
<td>0.08</td>
<td>0.68</td>
<td>-</td>
<td>0.001</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>110</td>
<td>102</td>
<td>-</td>
<td>101</td>
<td>110</td>
</tr>
<tr>
<td>SAI</td>
<td></td>
<td>-0.25</td>
<td>-0.16</td>
<td>0.33</td>
<td>-</td>
<td>-0.45</td>
</tr>
<tr>
<td></td>
<td>Significance Level P</td>
<td>0.010</td>
<td>0.12</td>
<td>0.001</td>
<td>-</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>101</td>
<td>94</td>
<td>101</td>
<td>-</td>
<td>101</td>
</tr>
<tr>
<td>25(OH)D nmol/L</td>
<td></td>
<td>0.19</td>
<td>0.008</td>
<td>-0.11</td>
<td>-0.45</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Significance Level P</td>
<td>0.02</td>
<td>0.93</td>
<td>0.23</td>
<td>-</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>141</td>
<td>102</td>
<td>110</td>
<td>101</td>
<td>-</td>
</tr>
</tbody>
</table>

Pearson correlation coefficient; BMI: Body mass index; SAI: sun avoidance inventory; BDI: Beck depression inventory; n: number of indoor employees.
Figure 2. Data comparison graph (box and whisker plots) of male versus female for BDI score, SAI score and 25(OH)D concentration.

make people avoid sun or even there could be another mediator factor between depression and sun avoidance behaviors. Further research to explore such relationships is needed. This is because the relation could be bi-directional. Shortage of sunlight or limited sun exposure could lead to depression (Grant et al., 2010). On the other hand, depressed lifestyles including loss of interest and the feelings of sadness tend to make depressed individuals prone to social withdrawal and being fairly house-bound. Studying such association is worthwhile, because the rate of depression is increasing globally at the same time when people start to avoid the sun exposure as a consequence of industrialization and urbanization (Sabetta et al., 2010). The lack of correlation between 25(OH)D and BDI may be explained by the relatively small sample size. Another explanation is that only about 10% of the sample had a vitamin D level >50 nmol/L, which makes it unlikely that any positive correlation would be detected. It is possible that the subjects under reported the psychological symptoms to avoid stigmatization or fear of jeopardizing their future employment prospects. However, the relationship between BDI and sun avoidance could be explained by other confounding variables, that is, low physical activity levels, behavioral withdrawal and sedentary life style may be associated with depressive episodes rather than vitamin D deficiency (Grant, 2009, 2011; Berk et al., 2007; Hoang et al., 2011; Hoogendijk et al., 2008; Jaddou et al., 2012; Opländer et al., 2009; Yapislar et al., 2012; Bertone-Johnson et al., 2011). Seasonal affective disorder is less likely as vitamin D levels are at peak during the winter months and do not change considerably during the year (Saadi et al., 2006; Saadi and Dawodu, 2007).

An interesting area of future research would be to look at the possible mutual exacerbation hypothesis. The sample as expected was chosen among normal office workers where depression rates are not expected to be high. Overall most of the subjects reported very few depressive symptoms and those with higher BDI scores were only marginally elevated (minor depression). However, looking at how the onset of depressive symptoms might increase sun avoidance or possibly lower vitamin D levels could prove informative to therapies aimed at alleviating depression. Depressed individuals tend to withdraw socially and deactivate behaviorally which may lead to social withdrawal and a sedentary indoor lifestyle.

Limitations in this study must be considered. For instance, convenience sampling was utilized. This is why our samples were not comparable in terms of age, gender and nationality. However, in terms of ethnicities, this sample is considered representative of populations in the UAE. According to the 2005 census, the total population of UAE was 4,798,491 million, of whom 19% were UAE nationals, 23% were Arabs, 50% were South
Asians, and 8% were Westerners (CIA-The World Factbook, 2009).

This study demonstrated that vitamin D deficiency is a major health concern among indoor employees in the UAE. As in previous studies, sun avoidance behaviors were the major risk factor for vitamin D deficiency in the UAE. Sun avoidance behaviors were also positively associated with depressive symptoms. Strategies to increase the stores of vitamin D should include vitamin D supplementation and fortification of food and drinks with vitamin D. An important public health message would be for indoor employees to take appropriate vitamin D supplements as well as ingesting food and drink fortified with vitamin D. Additionally, public awareness and education leading to changes in sun behaviors would also be highly desirable. Further research should be undertaken to explore the proposed links between vitamin D and chronic lifestyle disorders such as diabetes and depression.

ACKNOWLEDGEMENTS

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UPCOMING CONFERENCES

13th Congress of the Asia-Pacific Federation for Clinical Biochemistry and Laboratory Medicine (APCCB 2013), Bali, Indonesia, 27 Oct 2013

7th International Conference on Communication in Veterinary Medicine (ICCVM), St. Louis, USA, 4 Nov 2013
Conferences and Advert

**August 2013**
Association of Institutions for Tropical Veterinary Medicine (AITVM) 14th International Conference, Pretoria, South Africa, 25 Aug 2013

**September 2013**

**December 2013**
20th World congress on Parkinson's Disease and Related Disorders, Geneva, Switzerland, 8 Dec 2013