AIDS & HIV+ INFECTION

- Leptin as a possible modifier of Prostate Cancer in HIV-infected Males

- Association of Androgen Receptor Gene Polymorphism with HIV but not HCV Infection in Women

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LEPTIN AS A POSSIBLE MODIFIER OF PROSTATE CANCER IN HIV-INFECTED MALES

Introduction:
The leptin receptor is expressed in human peripheral mononuclear cells resulting in leptin stimulation of proliferation and activation and the prevention of apoptotic death in serum-deprived monocytes. Studies have shown an association between leptin levels and leptin gene mutations in patients with prostate cancer.

Since only 12 cases of prostate cancer have been described in patients with HIV infection and since leptin levels are generally low in patients with HIV infection, a study was initiated to investigate leptin and leptin genes and receptors in patients infected with HIV.

Methods:
DNA from 46 HIV infected male patients over 50 years of age receiving HAART, and 68 non-HIV infected patients with prostate cancer underwent PCR analysis. Genotyping was done on the genetic analyzer ABI3100 and the data obtained were analyzed using SPSS 10.1 software.

Results:
Comparative analyses of serum leptin, BMI and genotype frquency of LEPR and OBD7S1875 in both HIV and prostate cancer patients are listed below:

	HIV	PROSTATE CANCER	P_L
SERUM LEPTIN	LOW	HIGH	0.0001***
BMI	LOW	HIGH	0.006**
OBD7S1875	LONG ALLELES	SHORT ALLELES	0.015*
LEPR	SHORT ALLELES	LONG ALLELES	0.008**

Conclusions:
In this study positive correlations of high serum leptin levels and BMI were associated with short allele leptin and long allele leptin receptor genes in non-HIV infected patients with prostate cancer while HIV infected males were exactly opposite in all values with low serum leptin levels

and BMI and short allele receptors and long allele leptin genes. These data may prove to be associated with the reduced prevalence of prostate cancer in men over 50 with HIV infection.

ASSOCIATION OF ANDROGEN RECEPTOR GENE POLYMORPHISM WITH HIV BUT NOT HCV INFECTION IN WOMEN

Introduction:

Androgen deficiency is a common endocrine abnormality among men and women with human immunodeficiency virus (HIV) infection. Studies have shown the significant association of low testosterone and low circulating androgen concentrations in HIV infected men and women particularly with a reduction in lean body mass. Adrenal androgen is reduced in association with disease severity in HIV-infected women. During the last decade, a number of studies were undertaken to evaluate the significance of androgen receptor (AR) that belongs to the steroid hormone subfamily of nuclear hormone receptors and mediates the signal of androgens. About 25 percent of Americans with HIV also have HCV; the proportion may be as high as 90 percent among certain groups of people living with HIV disease.

About 10 percent of people with HCV also have HIV. Like HIV, HCV is transmitted by blood products and other body fluids. Until 1986, when routine testing in HCV of donated blood began, blood transfusions were responsible for the greatest number of HCV cases. Some studies have reported that people with co-infection have higher levels of hepatitis virus in their blood, more rapid progression of liver damage, and a greater rate of death due to hepatitis than people with only HCV infection.

Other recent research found no correlation between HCV progression and HIV status. Injection drug use, high body mass index, HCV infection, and use of psychotropic medications are associated with low androgen levels, and low androgen levels are associated with symptoms of hypogonadism. Androgens promote differentiation of mesenchymal multipotent cells into the myogenic lineage and inhibit their adipogenic differentiation, by facilitating association of androgen receptors with beta-catenin and activating T-cell factor 4. To confirm, the interference with the HCV co-infection and to examine the role of androgen in particular to HIV infection, androgen receptor gene polymorphism was screened in test groups with HIV, HCV HIV/HCV co-infection, and normal healthy subjects.

Methods:

DNA was isolated from 77 HIV, 26 HCV with monoinfection, 10 combined infections and 233 normal healthy subjects. Blood was drawn from test and control groups and DNA was isolated using standard procedure. An informed signed consent was obtained from all the study subjects. Polymorphisms in AR were genotyped by using the primers a) GRL22A 5'-ACATCCTGAGCGAGGCCAG- 3' b) GRL22B 5'-CCGACACTGCCTTACACAAC - 3' in polymerase chain reaction followed by HAE III restriction enzyme digestion(GG/CC).

Fragments were separated by electrophoresis on 10% polyacrylamide gel with ethidium bromide staining using appropriate commercially available size markers for comparison. Genotypes were designated as follows: complete cut with two bands as 22 (homozygous wild), partial cut with

three bands as 12 (heterozygous) and uncut as 11 (homozygous mutant). SPSS version 10.0 for Windows software (SPSS, Inc., Chicago, IL) was used for data analysis.

A Chi-Square test was used to compare categorical variables between groups. Frequency distribution of genotypes and alleles were determined in AR gene polymorphisms. Associations among these variables were determined using Spearman correlation coefficients. A P value of 0.05 was used to test for statistical significance, and all statistical tests were two tailed.

Results:

- In this study, we report the association of Androgen receptor gene polymorphism with HIV infection but not with HCV infection.
- A significant increase in homozygous 11 mutant genotype was observed in HIV individuals with mono (19.5%) and combined infections (30%; $p<.0001$).
- Individuals with only HCV infection did not show any variation (3.8%) in comparison to controls (3.1%)
- These data also shows that females with only HIV and combined infections had no heterozygous genotype as expected and such variation was not found in HCV females.

Conclusions:

- AR Gene polymorphism showed increased frequencies of the variant allele exclusively in patients with HIV monoinfection.
- The significant association of the homozygous mutant genotype-11 in HIV infected men and women could be a valuable marker to the treatment.
- The foregoing underscores the role of global genomic dysfunction that produces the progressive loss of cellular and glandular architecture, refractoriness to hormonal manipulation and increasing genomic instability.
- The collective experience of scientific studies to date supports the *polygenic* nature of this disease and its *individual-specific* clinical behavior.
- The key is to use more powerful methods to identify the specific genetic events and predisposing genetic markers.