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A pilot survey of aflatoxin-albumin adducts in sera from Egypt

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Keywords: aflatoxin, aflatoxin-albumin, biomarkers Egypt, serum

Short title: aflatoxin-albumin adducts in Egyptian sera

Abbreviations: aflatoxin B₁ (AFB₁), aflatoxin M₁ (AFM₁), aflatoxin-albumin (AF-alb), hepatocellular carcinoma (HCC), hepatitis B virus (HBV), hepatitis C virus (HCV),

Abstract

Aflatoxins are potent liver carcinogens that frequently contaminate dietary cereals within developing regions. Aflatoxin exposure has been predicted within Egypt but to date no studies have measured the level of aflatoxin-albumin (AF-alb) adducts as a validated biomarker to assess exposure. A limited number of sera were available from an hepatocellular carcinoma (HCC) case control study within Egypt. In this pilot survey AF-alb was detected in 24/24 samples from individuals without HCC diagnosis (geometric mean 9.0pg/mg range 3.5-25.8pg/mg), whilst 7/22 samples from HCC cases had detectable AF-alb (geometric mean 2.6pg/mg (range nd – 32.8pg/mg). These AF-alb data do not represent a case control comparison due to inherent difficulties in comparing markers of dietary intake between controls and patients with disease. Although these data are limited, the potential health consequences of aflatoxin exposure in this region merit further investigation.

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1 **Introduction**

2 Aflatoxins are metabolites of *Aspergillus flavus* and *parasiticus* which contaminate
3 common dietary staples during both cultivation and storage post-harvest (IARC 2002).
4 The most common and toxic of the naturally occurring aflatoxins is aflatoxin B₁
5 (AFB₁), and has been classified as a class 1A human liver carcinogen by the
6 International Agency of Research on Cancer (IARC 2002). The highest aflatoxin
7 exposures have been observed in parts of Africa, China and Southeast Asia, areas which
8 are also characterized by a high incidence of hepatocellular carcinoma (HCC) (IARC
9 2003). HCC is the fifth most common cancer in the world with around 500,000 new
10 cases annually, and HCC represents the third most common cause of cancer mortality in
11 the world (IARC 2003). The main risk factors for HCC in addition to aflatoxin are
12 hepatitis B virus (HBV) and hepatitis C viruses (HCV) (IARC 1994, 2002). Given the
13 burden of HCC in many regions of the world with mortality rates only slightly lagging
14 incidence rates, it is important to understand the contribution of all putative etiological
15 agents within a given region. In Egypt the prevalence of HCC is increasing (El-Zayadi
16 et al., 2005), and deaths due to HCC more than doubled in the previous two decades
17 increasing from 2.4 per 100,000 in 1987 to 5.2 per 100,000 in 2000 (El-Sawry et al.,
18 2001). Major etiological factors in this region are clearly HCV (Angelico et al., 1997;
19 Saeed et al., 1991; El-Zayadi et al. 2005, El-Kafrawy et al. 2005) and HBV (Attia,
20 1998), with a possible independent role for occupational pesticide exposures (Ezzat et
21 al. 2005). To date the potential role of aflatoxins in HCC development in Egypt has not
22 been fully explored. We recently reported that 8 of 41 liver samples from Egyptian
23 HCC cases contained a specific transversion mutation (AGG to AGT (arginine-to-
24 serine) at codon 249) within the TP53 tumour suppressor gene (TP53 Ser249) (El-
25 Kafrawy et al., 2005). This specific mutation is suggestive of aflatoxin being causative

for the mutation (Bressec et al., 1991; Hsu et al., 1991; Kirk et al., 2000). In response, we have undertaken a pilot biomarker survey to further assess the prevalence of aflatoxin exposure within Egypt. The level of aflatoxin-albumin (AF-alb) adduct in serum reflects the biologically effective aflatoxin dose, and serves as a useful aflatoxin exposure biomarker in humans (Sabbioni et al., 1987, Chapot and Wild 1991; Wild and Turner 2002). Moderate levels of aflatoxin exposure are predicted in Egyptian populations based on measures of the parent aflatoxins (or phase 1 metabolites) in biofluids (El-Nezami et al., 2000; Hatem et al., 2005; Hassan et al., 2006; Polychronaki et al., 2006, 2007a, 2007b). However, to date there has not been an assessment of aflatoxin exposure in Egypt using the more robust measure of the level of AF-alb adducts in serum. The AF-alb adduct is particularly valuable in this respect as it provides a good indicator of exposure over the previous two to three months (Montesano et al., 1999; Wild and Turner 2002). This manuscript describes an exploratory study in which the levels of AF-alb were measured for a subset of sera from individuals within an Egyptian HCC case-control study, previously reported by Ezzat et al., (2005). The prevalence and levels of exposure in this pilot study were compared to exposure patterns reported elsewhere.

Methods

Subject Recruitment

A case-control study was conducted from 1999 - 2004 to study viral and environmental risk factors associated with hepatocellular carcinoma (HCC) in Egypt. Detailed methods of recruitment have been previously documented (Cowgill et al. 2004; Ezzat et al. 2005). In brief the study consisted of 343 confirmed cases of HCC and 524 non-cancer controls matched by age, sex, and region of current residence. A subset of 46

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individuals, including 22 cases (aged 36-74; 18 males, 4 females) and 24 controls (aged 37-73; 20 males, 4 females), for whom blood samples were available, were tested for the level of serum AF-alb adduct. All of these individuals were from the Cairo metropolitan area or governorates within the Nile Delta, and all were HBsAg negative. The subset of cases for this AF-albumin study were selected because they had TP53 gene mutation results available from a previous analysis (El-Kafrawy et al. 2005); controls were randomly selected from the total pool of controls to match these cases on age, gender and region distributions. However, due to difficulties in comparing biomarkers related to dietary intake where one group are patients with disease, this manuscript is not attempting to present case control data in relation to HCC causation.

AF-albumin ELISA

The levels of AFB₁-albumin adduct were determined by albumin extraction, digestion and ELISA as previously described (Chapot and Wild 1991). The detection limit was 3pg AFB₁-lysine equivalents per mg of albumin (pg/mg). Three positive and one negative control samples were analyzed with each batch of samples. Samples were measured in quadruplicate on two separate days; CVs were less than 25%. AF-alb data were natural log transformed to better approximate a normal distribution. Table 1, reports the percentage of Egyptian samples with detectable AF-alb, and for clarity adduct levels are back transformed and presented as geometric means.

Results and Discussion

Aflatoxin is a potent hepatocarcinogen, and given that exposure can occur throughout life it is important to understand the pattern of exposure in regions potentially at risk from this toxin. AF-alb has been used as a specific biomarker of exposure in West

1 African adults (Wild et al., 2000; Turner et al., 2005a; Dash et al., 2007) and children
2 (Turner et al., 2000, 2003, 2005b, 2007; Gong et al., 2002, 2004), and exposure based
3 on this biomarker is frequent and at high levels. By comparison, there is less
4 information from Egypt on aflatoxin exposure using biomarkers but levels are predicted
5 to be lower than in West Africa (El-Nezami et al., 2000; Hatem et al., 2005). In this
6 pilot study of Egyptian samples, AF-alb adducts were detected in 31 of 46 (67.4%) of
7 the samples (geometric mean 5.0pg/mg (range non detectable to 32.8pg/mg), see Table
8 1. Of the 24 individuals without HCC, all were positive for AF-alb (n=24, geometric
9 mean 9.0pg/mg; range 3.5 – 25.8pg/mg. By contrast fewer individuals, 7 of 22 (31.8%),
10 with HCC had detectable adducts, and overall adduct levels were lower ($p<0.001$) in
11 cases (geometric mean 2.6pg/mg; range non detectable to 32.8pg/mg). HCC is
12 frequently diagnosed late, and due to the advanced state of the disease it is known that
13 individuals diagnosed with HCC in Africa have modified or restricted diets, leading to
14 lower aflatoxin exposures (Kirk et al., 2005). Dietary surveys were not conducted
15 within this study to specifically address this issue. AF-alb adducts were not observed for
16 the eight HCC cases carrying the TP53 Ser249 mutation, which may again simply
17 reflect such changes in dietary intake for HCC cases. In addition, if aflatoxin exposure
18 were causative for the reported TP53 Ser249 mutations in these eight HCC cases, this
19 would be as a consequence of chronic exposure over years or decades, thus a measure of
20 recent exposure would not necessarily correlate with the mutation (Kirk et al., 2005).

21 For the non HCC cases, a non-significant trend ($p>0.05$) towards higher adduct levels
22 was observed for those from rural areas (geometric mean 11.2pg/mg; 95%CI: 7.7,
23 16.2pg/mg, n= 9) compared to those in urban areas (geometric mean 7.9pg/mg; 95%CI:
24 5.8, 10.7, n=15), possibly reflecting less varied diets and reliance on basic dietary
25 staples in rural settings, as observed in The Gambia (Wild et al., 2000). A similar but

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1 again non-significant trend was also observed within the cases (data not shown).
2 Numbers limit both the interpretation of this observation, and further analysis of the
3 data by age, sex, or seasonality.

4 A comparison of AF-alb adducts in this study and a number of other countries,
5 measured using the ELISA methodology, are made in Table 1. The frequency and level
6 of exposure in West African countries is clearly higher, and for many individuals in
7 West Africa the levels exceed 100pg/mg (Wild et al, 2000; Turner et al., 2007). A
8 similar high prevalence of AF-alb was reported for adults in Ghana (Dash et al., 2007),
9 however, differences in assay methodology restrict further comparison with their data.
10 Limited surveys in Western Europe revealed no positive samples for this adduct
11 (reviewed by Wild et al., 1993). The frequency and levels of exposure in these Egyptian
12 samples are therefore considered to be intermediate in comparison with the low risk and
13 high risk areas for exposure, and to be more in line with exposures recently observed by
14 Scussel et al., (2006) in Brazil, or previously reported from Thailand (reviewed by Wild
15 et al., 1993).

17 Urine samples and breast milk provide additional bio-fluids with which to monitor
18 aflatoxin exposure. AFM₁ is a major metabolite of AFB₁ and is the main aflatoxin that
19 is sequestered into breast milk following maternal exposure to AFB₁ (Zarba et al., 1992;
20 IARC 2002). The frequency of AF-alb in our present study are in line with recent
21 observations of aflatoxin M₁ in breast milk samples from Egyptian mothers
22 (Polychronaki et al., 2006) in which 138/388 (35.6%) were positive for this metabolite.
23 The difference in prevalence may reflect the longer half-life of the albumin adduct,
24 approximately 3 weeks (Chapot and Wild, 1991), compared to AFM₁.

Depending on sex and geographic location within Egypt the HBV surface antigen (indicative of current infection) was detected in 3-11% of the total case-control study population (Ezzat et al., 2005), and HBV was estimated to contribute 5-10% to the burden of HCC in Egypt. In regions where co-exposure to aflatoxin and chronic carriage of HBV infection occur, a synergistic interaction in the development of HCC has been reported (Ross et al., 1992; Qian et al., 1994; Wang et al., 2001), with the relative risk of HCC increasing up to 60-fold with co-exposure. Given the level of chronic HBV carriage in Egypt, the significance of potential co-exposure to aflatoxin is of concern. HCV accounts for nearly 90% of the HCC burden in Egypt (Ezzat et al., 2005), however, to date no interaction between HCV infection and aflatoxin exposure are reported in the literature.

The purpose of this survey was a pilot investigation of the prevalence of AF-alb adducts, as a biomarker of aflatoxin exposure, within Egypt. To our knowledge the measurement of this validated biomarker to assess exposure in this region has not previously been reported. Our data indicate moderate levels of aflatoxin exposure is occurring within this limited survey, though larger studies are needed to investigate both the sources and potential consequences of exposure to this potent toxin in Egypt.

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Table 1: Aflatoxin-albumin adducts in adults from selected countries.

COUNTRY (n)	AF-Alb (pg/mg) Geometric Mean (range)	Prevalence of positive samples (%)	Reference
Egypt			This report
Total	5.0 (nd – 32.8)	31/46 (76)	
HCC cases	2.6 (nd – 32.8)	7/22 (31.8)	
Controls	9.0 (nd – 25.8)	24/24 (100)	
The Gambia			
Rural	61.8 (57.3 – 66.7)#	272/272 (100)	Wild et al., 2000
Peri-urban	39.1 (31.1 – 49.1)#	83/84 (98.8)	
Guinea##	18.4 (nd-66)	245/250 (98)	Turner et al., 2005b
The Gambia	40.4 (4.8-260.8)	119/119 (100)	Turner et al., 2007
Brazil*	10.7 (nd – 57.3)	31/59 (62)	Scussel et al., 2006
France/ Poland	0 (nd)	0/74 (0)	Wild et al., 1993

nd. non-detected
* Geometric means of positives only
Geometric means and 95%CI
Data obtained for blood samples in Feb/Mar
\$ - Infants aged 4 months old.

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